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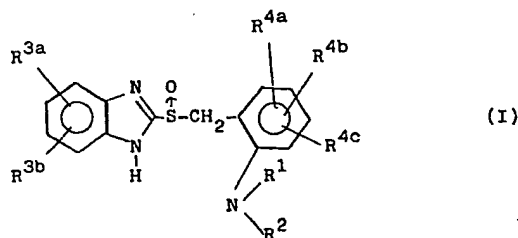
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Stabilized benzimidazole derivative and composition.

A stabilized physiologically active benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a

halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group. The stabilized benzimidazole derivative is in amorphous form or present in contact with a basic material.

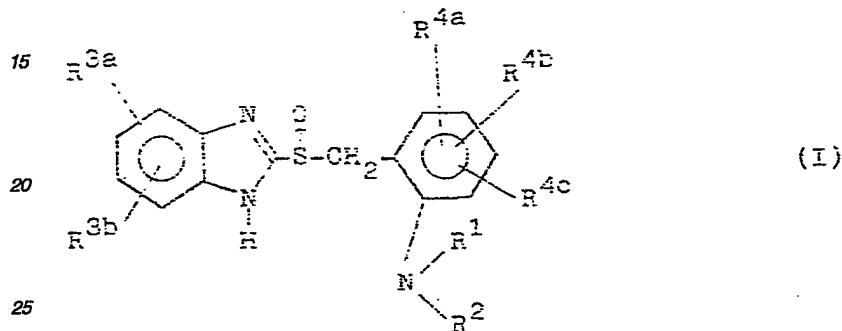
## Description

STABILIZED BENZIMIDAZOLE DERIVATIVE AND COMPOSITIONBACKGROUND OF THE INVENTIONField of the invention

This invention relates to a stabilized benzimidazole derivative and a composition in which a benzimidazole derivative is stabilized.

Description of prior art

There is known a physiologically active benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group.

The benzimidazole derivative of the formula (I) shows a prominent inhibitory action on secretion of gastric acid as is described in GB 2,161,160A and GB 2,163,747A (corresponding to DE 3,531,487A1). Moreover, some benzimidazole derivatives of the formula (I) can be employed as cytoprotective agents for gastrointestinal tract.

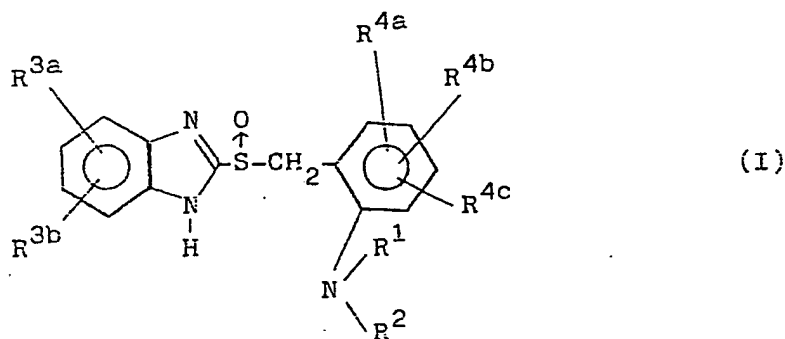
SUMMARY OF THE INVENTION

The present inventors have made study for actually utilizing the benzimidazole derivative of the formula (I) as a physiologically active component of a pharmaceutical and found that these benzimidazole derivative is poor in storage stability.

Accordingly, an object of the present invention is to provide a physiologically active benzimidazole derivative of the formula (I) which is improved in storage stability.

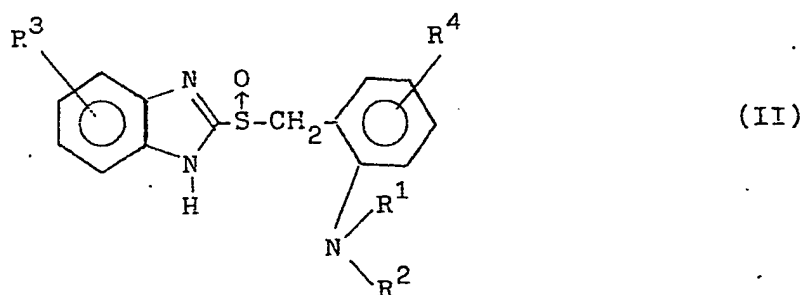
Another object of the invention is provide a composition containing a physiologically active benzimidazole derivative under stabilized condition.

There is provided by the present invention a physiologically active benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group, which is in amorphous state or is kept in contact with an organic or inorganic basic material.

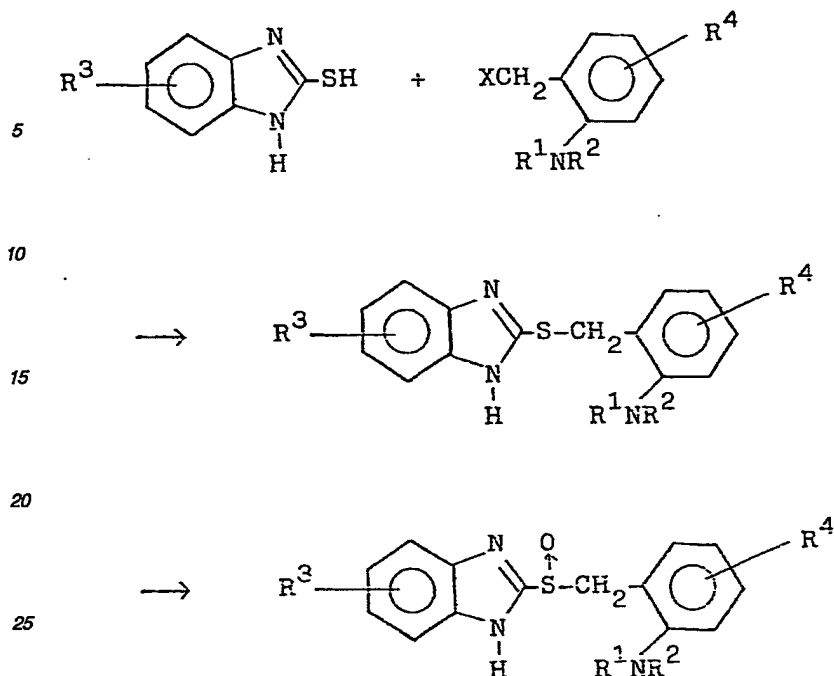
Particularly, the present invention provides a stabilized physiologically active benzimidazole derivative of the formula (II):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group, which is in amorphous state or is kept in contact with an organic or inorganic basic material.

#### DETAILED DESCRIPTION OF THE INVENTION

The benzimidazole derivatives of the formula (I) can be prepared by known processes. For instance, the benzimidazole derivative of the formula (II) can be prepared by the process according to the following equation:



30 wherein X is a reactive group and each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> has the same meaning as defined hereinbefore. The benzimidazole derivatives of the formula (I) other than the derivative of the formula (II) can be prepared in similar manners.

Representative examples of the compounds of the formula (I) include:

- 35 Compound 1: 2-(2-dimethylaminobenzylsulfinyl)benzimidazole,  
 Compound 2: 2-(2-diethylaminobenzylsulfinyl)benzimidazole,  
 Compound 3: 2-(2-aminobenzylsulfinyl)benzimidazole,  
 Compound 4: 2-(2-methylaminobenzylsulfinyl)benzimidazole,  
 Compound 5: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxybenzimidazole,  
 40 Compound 6: 2-(2-diethylaminobenzylsulfinyl)-5-methoxybenzimidazole,  
 Compound 7: 2-(2-dimethylamino-6-methylbenzylsulfinyl)benzimidazole,  
 Compound 8: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxycarbonylbenzimidazole,  
 Compound 9: 2-(2-dimethylaminobenzylsulfinyl)-5-methylbenzimidazole,  
 Compound 10: 5-chloro-(2-dimethylaminobenzylsulfinyl)benzimidazole,  
 45 Compound 11: 5-amino-(2-dimethylaminobenzylsulfinyl)benzimidazole,  
 Compound 12: 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole,  
 Compound 13: 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole,  
 Compound 14: 2-(2-piperidinobenzylsulfinyl)benzimidazole,  
 Compound 15: 2-[2-(N-cyclohexyl-N-methylamino)benzylsulfinyl]benzimidazole, and  
 50 Compound 16: 2-[2-(N-benzyl-N-methylamino)benzylsulfinyl]benzimidazole.

The benzimidazole derivative employed in the present invention preferably is a compound having the formula (I) wherein R<sup>1</sup> is an alkyl group containing 1-8 carbon atoms. R<sup>2</sup> preferably is a lower alkyl group. Preferably, each of R<sup>3a</sup> and R<sup>3b</sup> is independently hydrogen atom or an alkoxy group. Preferably, each of R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> is independently is hydrogen atom or a lower alkyl group. In the specification, the lower alkyl group and the lower alkoxy group mean those containing 1-6 carbon atoms.

55 As a result of the study of the present inventors, it has found that the benzimidazole derivative of the formula (I), which is prepared in the form of crystals according to known processes for the preparation, can be prominently improved in storage stability when it is formed in amorphous state.

The benzimidazole derivative of the formula (I) can be converted into a amorphous compound, for instance, by freezing a crystalline compound in an organic solvent and then evaporating the solvent. However, it is advantageous to treat the crystalline compound in such a manner that the crystalline compound is dissolved in an organic solvent containing an organic polymer and then forcing to remove the solvent through evaporation or that the crystalline compound is dissolved in an organic solvent containing an organic polymer and then spray-drying the resulting solution.

65 In the above process, there is no need of dissolving the benzimidazole derivative and/or the organic polymer

in the solvent. For instance, the benzimidazole derivative and/or organic polymer can be suspended in the organic solvent. For this reason, the organic solvent can be replaced with an aqueous organic solvent or replaced simply with water. In the case that water or an aqueous organic solvent is employed as the solvent, the organic polymer preferably is water-soluble. Further, in the case that water or an aqueous organic solvent is utilized, a surface active agent can be utilized as a dispersant.

Examples of the organic polymers employable for converting a crystalline benzimidazole derivative into an amorphous benzimidazole derivative include synthetic or natural polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch, agar and  $\alpha$ -cyclodextrin. Preferred are cellulose derivatives.

As described above, the organic polymer preferably is a water soluble polymer in the case the solvent is water or an aqueous organic solvent. Examples of the water-soluble polymers include carboxymethylcellulose sodium, poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch, and agar.

The organic polymer is preferably utilized in an amount of not less than 0.5 time, more preferably not less than 2 times as much as a weight of the benzimidazole derivative.

There is no limitation with respect to the organic solvent employed for the preparation of a solution of the benzimidazole derivative and the organic polymer, so long as the derivative and the polymer are dissolved in the solvent. Advantageously employable are alcohols and halogenated alkyls. As described above, the organic solvent can be used in combination with water and optionally with a surface active agent.

It is not known why the benzimidazole derivatives of the formula (I) are prominently improved in the storage stability by converting a crystalline product into an amorphous product. However, it can be thought as follows.

It is observed that the benzimidazole derivative of the formula (I) emits strong heat when it decomposes. Accordingly, it is assumed that when the benzimidazole derivative in crystalline state once starts decomposition locally at a certain area, decomposition is extended rapidly to other area by way of heat produced by the strong exothermic reaction. In amorphous state, the local decomposition of the benzimidazole derivative is extended slowly to other area because the produced heat is not transmitted to the surrounding area rapidly.

It is further assumed that the organic polymer introduced into the benzimidazole derivative composition serves for forcing the formation of an amorphous compound in the conversion procedure and further serves in the composition as a barrier between the resulting amorphous particles for suppressing transmission of heat from the decomposed area to other area, whereby further improving the storage stability of the benzimidazole derivative.

According to the present invention, the improvement of storage stability of the benzimidazole derivative of the formula (I) can be accomplished by bringing the derivative into contact with and a basic material in an amount of not less than 5 weight %, preferably not less than 10 weight %, more preferably in the range of 10 to 200 weight %, based on an amount of the benzimidazole derivative. For instance, the contact between the benzimidazole derivative and the basic material can be attained by preparing a composition containing both the benzimidazole derivative and the basic material.

The basic material used herein means a material which shows pH 7 or higher, preferably pH 8 or higher, in the form of an aqueous solution or an aqueous suspension.

The basic material preferably is a hydroxide or a salt with a weak inorganic acid of a metal such as an alkali metal, an alkaline earth metal and aluminum. More concretely, the basic material preferably is a hydroxide such as alumina magnesium hydroxide ( $2.5Al_2O_3 \cdot Mg(OH)_2$ ), aluminum hydroxide and magnesium hydroxide. Examples of the salts with a weak inorganic acid include carbonates such as potassium carbonate, calcium carbonate, sodium hydrogen carbonate and magnesium carbonate; phosphates such as potassium monohydrogen phosphate, potassium phosphate and sodium phosphate; and coprecipitation products of hydroxide with carbonate such as aluminum hydroxide-sodium hydrogen carbonate coprecipitation product and aluminum hydroxide-magnesium carbonate-calcium carbonate coprecipitation product.

The basic material may be a salt of an organic acid (e.g., higher fatty acid) with an alkali metal, an alkaline earth metal, aluminum and amine. The basic material may be an amide, a basic amino acid, a thiamine and an amine. Examples of the organic acids are fatty acids having 12-22 carbon atoms, benzoic acid, alginic acid, edetic acid (EDTA), citric acid, glycyrrhizic acid, glutamic acid, gluconic acid, succinic acid, fumaric acid, salicylic acid, and lactic acid. Preferred are higher fatty acids having 12-22 carbon atoms such as stearic acid, palmitic acid and myristic acid. Examples of the metals, include sodium, potassium, calcium, magnesium, and aluminum. Examples of the amines include isopropanolamine, diphenylamine, ethanolamine, and benzylamine.

Preferred salts of organic acids with an alkali metal, an alkaline earth metal and aluminum are sodium stearate, potassium stearate, magnesium stearate, aluminum stearate, sodium palmitate, potassium palmitate, magnesium palmitate, aluminum palmitate, sodium myristate, potassium myristate, magnesium myristate, aluminum myristate, sodium benzoate, sodium alginate, sodium edetate, sodium citrate, sodium glycyrrhizinate, potassium glycyllsinate, sodium glutamate, sodium gluconate, potassium gluconate, sodium succinate, sodium fumarate, sodium salicylate, and calcium lactate.

Examples of the amides include nicotinic amide and monomethylnicotinic amide. An example of the basic amino acid is histidine. An example of the thiamine is vitamin B<sub>1</sub>. Examples of the amines include

diisopropanolamine, diphenylamine, ethanolamine and benzylamine.

In the composition containing both the benzimidazole derivative of the formula (I) and a basic material, the benzimidazole derivative preferably is present in the form of particles preferably having a mean diameter of not more than 10  $\mu\text{m}$ . The benzimidazole derivative of the formula (I) is more stable when it is in the form of such fine particles.

The benzimidazole derivative can be converted into fine particles using known micronizers for the preparation of fine particles. Examples of such micronizers include mechanical micronizers such as pin mill, attrition mill, screw crusher, ring roller mill, ball mill; and hydromechanical energy micronizers such as jet mill, jet pulverizer, micronizer, reductionizer jet pulverizer and air mill.

The stabilized amorphous benzimidazole derivative and the composition of the stabilized benzimidazole derivative shows prominent inhibitory action on secretion of gastric acid and also is employable as a cytoprotective agent for gastrointestinal tract. The stabilized benzimidazole derivative of the formula (I) and the composition containing the stabilized benzimidazole derivative can be administered orally or parenterally. Examples of the preparation forms for oral administration include tablets, capsules, powder, granules, and syrup. In the formulation of these preparations, there can be used excipients, disintegrants, binders, lubricants, pigments, diluents and the like which are commonly used in the art. Examples of the excipients include glucose, sucrose, lactose, and microcrystalline cellulose. Examples of the disintegrants include starch and carboxymethylcellulose calcium. Examples of the lubricants include hardened oil and talc. Examples of the binders include hydroxypropylcellulose, gelatin and polyvinylpyrrolidone. Other additives can be also used.

The dose is generally not more than 500 mg/day, preferably about 100  $\mu\text{g}$ /day to 300 mg/day, for an adult. This value is expressed in terms of the amount of the physiologically active compound, namely the benzimidazole derivative of the formula (I). The dose can be either increased or decreased depending upon the age and other conditions.

The present invention is further described by the following examples.

#### Synthesis of 2-(2-Dimethylaminobenzylsulfanyl)benzimidazole

##### (1) 2-(2-Dimethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (4.73 g) was dissolved in 150 ml of ethanol, and to the solution was added 6.18 g of 2-dimethylaminobenzyl chloride hydrochloride. The mixture was stirred at room temperature for 30 minutes. Precipitated crystals were collected by filtration. A saturated aqueous  $\text{NaHCO}_3$  solution was added to the crystals, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from a mixture of chloroform and acetonitrile to obtain 5.39 g of 2-(2-dimethylaminobenzylthio)benzimidazole as a colorless crystalline product (m.p. 164°C).

##### (2) 2-(2-Dimethylaminobenzylsulfanyl)benzimidazole

2-(2-Dimethylaminobenzylthio)benzimidazole (4.8 g) was dissolved in a mixture of 40 ml of chloroform and 5 ml of methanol. After the solution was chilled to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added portionwise. Ten minutes later, a saturated aqueous  $\text{NaHCO}_3$  solution was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The chloroform solution was washed with saturated brine and then dried over anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure and the residue was recrystallized from a mixture of chloroform and ether to obtain 2.97 g of 2-(2-dimethylaminobenzylsulfanyl)benzimidazole as a colorless crystalline product (m.p. 116°C, decomposed).

#### Example 1

In 10 ml of methyl alcohol were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfanyl)benzimidazole and 3.0 g of hydroxypropylcellulose. The resulting solution was placed in a rotary evaporator for concentration. The concentrated residue was poured in a Petri dish, and placed overnight in a vacuum dryer at 35°C. The dried composition product was in the form of a pale yellow film.

The composition in the form of a film was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

#### Example 2

In 100 ml of chloroform were dissolved 3.0 g of the colorless 2-(2-dimethylaminobenzylsulfanyl)benzimidazole and 9.0 g of poly(vinylpyrrolidone). The resulting solution was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 3.5 ml/min. and a temperature of supplied air at 100°C, to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

Example 3

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

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Example 4

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

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The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

Example 5

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The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of methylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

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Example 6

In 30 ml of methylene chloride were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfanyl)benzimidazole and 1.0 g of a nonionic surface active agent (low HLB type) to obtain an oily solution. Independently, in 250 ml of water were dissolved 3.0 g of carboxymethylcellulose sodium and 1.0 g of a nonionic surface active agent (high HLB type) to obtain an aqueous solution.

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The oily solution and the aqueous solution were combined and violently mixed to give an emulsion. The resulting emulsion was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 2.0 ml/min. and a temperature of supplied air at 120°C, to obtain a fine powdery composition.

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The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in amorphous state.

Comparison Example 1

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In a mortar were mixed 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfanyl)benzimidazole and 3.0 g of hydroxypropylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in crystalline state.

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Comparison Example 2

The procedure of Comparison Example 1 was repeated except for replacing the hydroxypropylcellulose with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole in the composition was in crystalline state.

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Evaluation on Storage Stability

The 2-(2-dimethylaminobenzylsulfanyl)benzimidazole-containing compositions obtained in Examples were stored in a thermostat at 70°C for 6 days. In the course of the storage, an amount of 2-(2-dimethylaminobenzylsulfanyl)benzimidazole remaining in the composition (i.e., remaining amount) was determined at lapse of 2 days, 4 days, and 6 days, to evaluate storage stability of 2-(2-dimethylaminobenzylsulfanyl)benzimidazole.

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The remaining amount of 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was determined by taking out approx. 900 mg of the stored sample, weighing the taken sample, adding methanol to the sample to make a total volume of precisely 100 ml under shaking for extraction by methanol, diluting the methanolic extract to make a total volume of 100 times as much as the methanolic extract, subjecting 20 µl of the diluted solution to determination based on HPLC (high pressure liquid chromatography) method.

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The results are set forth in Table 1. The numerals in Table 1 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfanyl)benzimidazole.

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Table 1

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Sample	Period of Storage			
	0 day	2 days	4 days	6 days
Example 1	100	98.2	96.6	86.6
Example 2	100	99.8	99.4	95.5
Example 3	100	99.5	98.8	99.2
Example 4	100	96.2	93.6	79.0
Example 5	100	95.5	90.0	85.3
Example 6	100	98.9	97.3	95.4
Com. Ex. 1	100	94.8	87.2	56.2
Com. Ex. 2	100	94.1	82.5	44.1

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Examples 7 - 14

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm<sup>2</sup> and rate of 1 kg/hr to obtain a white microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (decomposition point: 121-127°C, mean diameter 2 μm) in 95 % yield.

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The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was mixed with a basic material set forth in Table 2 at weight ratio of 1 : 1. The resulting composition was stored at 50°C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfinyl) benzimidazole was determined in the same manner described above.

The results are set forth in Table 2.

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Comparison Example 3

The procedure of Example 7 was repeated except that no basic material was mixed, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

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Comparison Examples 4 - 11

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 2, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

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Table 2

Sample	Added Material	Remaining amount (%)	
Example 7	Alumina magnesium hydroxide	88.1	15
Example 8	Sodium carbonate	94.7	
Example 9	Calcium hydrogen phosphate	95.8	
Example 10	Aluminum hydroxide	80.8	20
Example 11	Magnesium methasilicate aluminate	51.1	
Example 12	Anhydrous calcium phosphate	97.4	
Example 13	Magnesium carbonate	78.9	25
Example 14	Sodium hydrogen carbonate	81.2	
Com. Ex. 3	-----	1.7	30
Com. Ex. 4	Calcium sulfate	4.1	
Com. Ex. 5	Lactose	0.8	35
Com. Ex. 6	D-Mannitol	0.9	
Com. Ex. 7	Microcrystalline cellulose	10.5	
Com. Ex. 8	Corn starch	3.0	40
Com. Ex. 9	Polyethylene glycol	1.0	
Com. Ex. 10	Methylcellulose	1.4	
Com. Ex. 11	Succinic acid	0.0	45

Remarks: The numerals in Table 2 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfiny)benzimidazole.

#### Examples 15 - 17

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 3 and the storage period was changed to 30 days, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfiny)benzimidazole. The results are set forth in Table 3.

Table 3

Sample	Added Material	Remaining amount (%)
Example 15	Alumina magnesium hydroxide	51.6
Example 16	Aluminum hydroxide	37.3
Example 17	Magnesium carbonate	55.0

Remarks: The numerals in Table 3 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 18 & 19 and Comparison Examples 12-13

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole prepared in Example 7 was mixed with additives set forth in Table 4 to obtain a 2-(2-dimethylaminobenzylsulfinyl)benzimidazole-containing composition.

Table 4

	Example		Comparison
	18	19	Example 12
Benzimidazole derivative	30	30	30
Lactose	47	37	57
Corn starch	10	10	10
Alumina magnesium hydroxide	10	20	-
Hydroxypropylcellulose	3	3	3

In Table 4, the numerals are expressed in terms of weight parts.

The resulting compositions and an untreated microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (for Comparison Example 13) were kept at 50°C, 75%RH for 5 days, 10 days and 20 days, for evaluating storage stability in the same manner as described above.

The results are set forth in Table 5. The numerals in Table 5 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Table 5

Sample	Period of Storage			
	0 day	5 days	10 days	20 days
Example 18	100	99.6	95.2	93.4
Example 19	100	99.6	94.8	92.9
Com. Ex. 12	100	99.7	95.6	66.0
Com. Ex. 13	100	95.1	1.6	-

Examples 20 - 22

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm<sup>2</sup> and rate of 1 kg/hr to obtain a white microcrystalline 2-(2-dimethylaminobenzylsulfanyl)benzimidazole (decomposition point: 121-127°C, mean diameter 2  $\mu$ m) in 95 % yield.

The microcrystalline 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was mixed with a basic material set forth in Table 6 at weight ratio of 1 : 1. The resulting composition was stored at 50°C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was determined in the same manner described above.

The results are set forth in Table 6.

Table 6

Sample	Added Material	Remaining amount (%)
Example 20	Nicotinamide	64.6
Example 21	Magnesium stearate	63.3
Example 22	Calcium stearate	35.8

Remarks: The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfanyl)benzimidazole.

Examples 23 & 24

The procedure of Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzyl)sulfanyl)benzimidazole (for Example 23) and 2-(2-dimethylamino-5-methylbenzyl)sulfanyl)benzimidazole (for Example 24) and the amount of hydroxy propyl

cellulose was changed into 5.0 g., to obtain an amorphous product. The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 and 8.

5 Examples 25 & 26

The procedure of Example 7 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Example 25) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Example 26). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

10 Examples 27 & 28

The procedure of Example 21 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Example 27) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Example 28). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

15 Comparison Examples 14 & 15

The procedure of Comparison Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Comparison Example 14) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 15). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

20 Comparison Examples 16 & 17

The procedure of Comparison Example 5 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Comparison Example 16) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 17). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

25 Comparison Examples 18 & 19

The procedure of Comparison Example 11 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Comparison Example 18) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 19). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

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Table 7  
[2-(2-dimethylamino-5-methoxybenzyl)sulfinylbenzimidazole]

Sample	Storage Period		
	0 day	5 days	10 days
Example 23	100	99.8	99.5
Example 25	100	99.2	95.9
Example 27	100	99.6	96.9
Com. Ex. 14	100	98.3	74.6
Com. Ex. 16	100	99.2	78.1
Com. Ex. 18	100	0	-
Ref. Ex. 1	100	99.4	76.3

Remarks: Sample of Ref. Ex. 1 is an untreated microcrystalline 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.  
The numerals in Table 7 mean relative amounts of the remaining 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.

Table 8

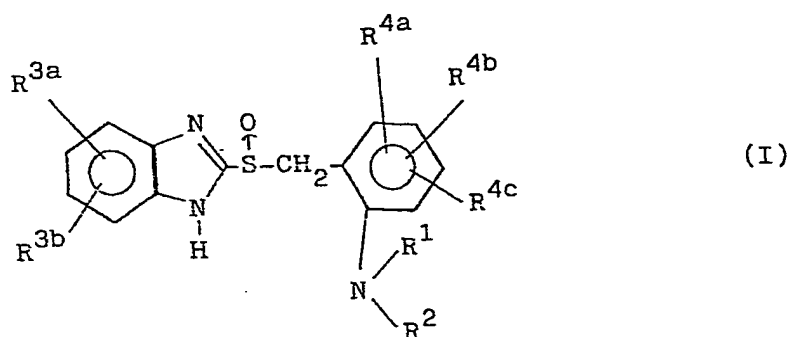
[2-(2-dimethylamino-5-methylbenzyl)sulfinylbenzimidazole]

Sample	Storage Period		
	0 day	5 days	10 days
Example 24	100	99.2	99.2
Example 26	100	75.4	49.5
Example 28	100	87.5	71.8
Com. Ex. 15	100	9.9	4.5
Com. Ex. 17	100	60.1	0.1
Com. Ex. 19	100	0	-
Ref. Ex. 2	100	30.4	10.0

Remarks: Sample of Ref. Ex. 2 is an untreated microcrystalline 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.  
The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.

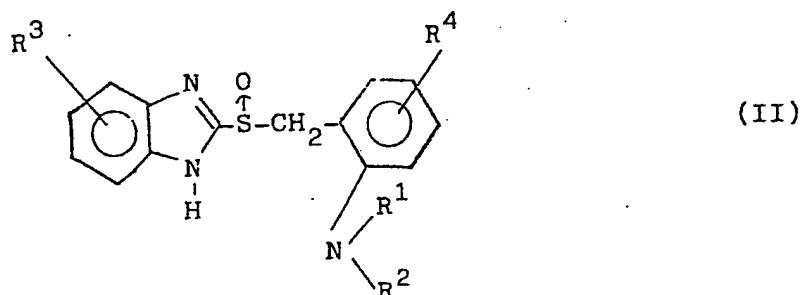
## Claims

1. A physiologically active benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group, which is in amorphous state.

2. The benzimidazole derivative as claimed in claim 1, wherein the benzimidazole derivative has the formula (II):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

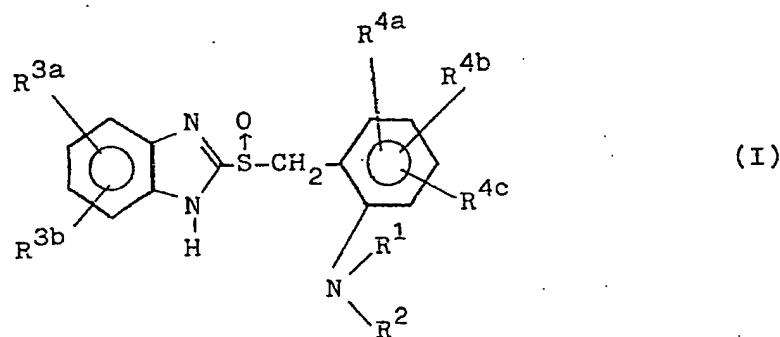
3. The benzimidazole derivative as claimed in claim 1, wherein R<sup>1</sup> of the formula (I) representing the benzimidazole derivative is an alkyl group containing 1 to 8 carbon atoms.

4. The benzimidazole derivative as claimed in claim 1, wherein R<sup>2</sup> of the formula (I) representing the benzimidazole derivative is a lower alkyl group.

5. The benzimidazole derivative as claimed in claim 1, wherein each of R<sup>3a</sup> and R<sup>3b</sup> of the formula (I) representing the benzimidazole derivative is hydrogen atom or a lower alkoxy group.

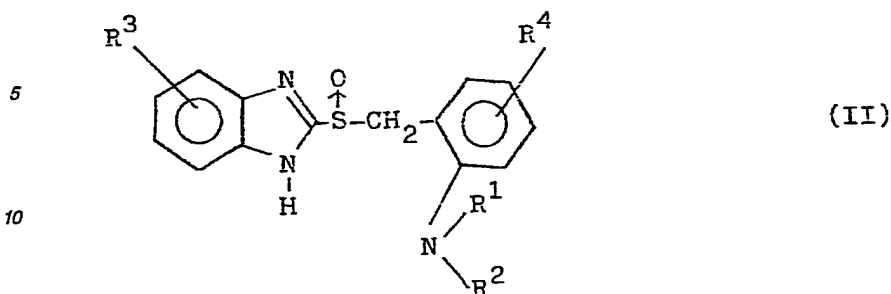
6. The benzimidazole derivative as claimed in claim 1, wherein each of R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> of the formula (I) representing the benzimidazole derivative is hydrogen atom or a lower alkyl group.

7. A composition containing a physiologically active amorphous benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, dispersed in an organic polymer.

8. The composition as claimed in claim 7, wherein the benzimidazole derivative has the formula (II):



20 wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

25 9. The composition as claimed in claim 7, wherein the organic polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch and agar.

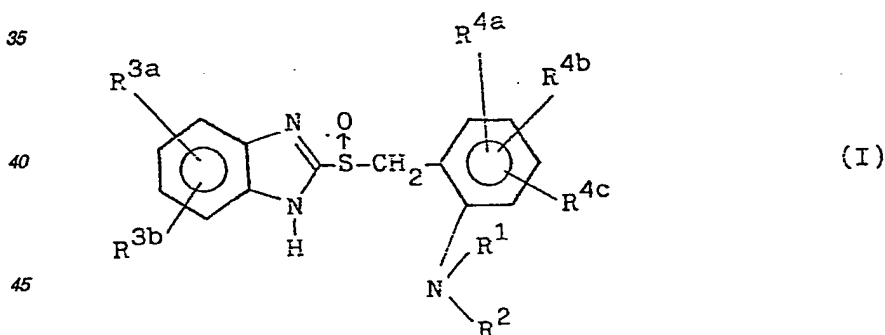
30 10. The composition as claimed in claim 7, wherein the organic polymer is a cellulose derivative.

11. The composition as claimed in claim 7, wherein the organic polymer is a water soluble polymer.

12. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 0.5 time as much as a weight of the benzimidazole derivative.

13. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 2 times as much as a weight of the benzimidazole derivative.

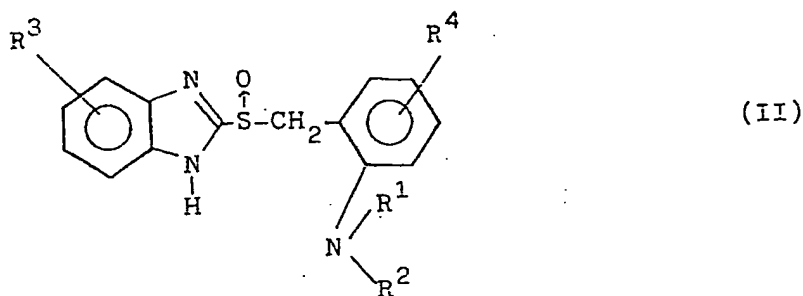
14. A composition containing a physiologically active benzimidazole derivative having the formula (I):



50 wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, and a basic material in an amount of not less than 5 weight % based on an amount of the benzimidazole derivative.

55 15. The composition as claimed in claim 14, wherein the benzimidazole derivative has the formula (II):





wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxy carbonyl group or an amino group.

16. The composition as claimed in claim 14, wherein the basic material is a hydroxide or a salt with a weak inorganic acid of a metal selected from the group consisting of an alkali metal, an alkaline earth metal and aluminum.

17. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of alumina magnesium hydroxide, aluminum hydroxide and magnesium carbonate.

18. The composition as claimed in claim 14, wherein the basic material is a salt of an organic acid with an alkali metal, an alkaline earth metal, aluminum and amine.

19. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of amide, basic amino acids, thiamines and amines.

20. The composition as claimed in claim 14, wherein the basic material is a salt of a higher fatty acid with an alkali metal or an alkaline earth metal.

21. The composition as claimed in claim 14, wherein the basic material is contained in an amount of not less than 10 weight % based on an amount of the benzimidazole derivative.

22. The composition as claimed in claim 14, wherein the basic material is contained in an amount of 10 to 200 weight % based on an amount of the benzimidazole derivative.

23. The composition as claimed in claim 14, wherein the benzimidazole derivative is contained in the form of particles having a mean diameter of not more than 10  $\mu$ m.

(19)



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(56) References cited:  
**EP-A- 0 174 717**  
**EP-A- 0 204 215**  
**EP-A- 0 218 336**  
**GB-A- 2 163 747**

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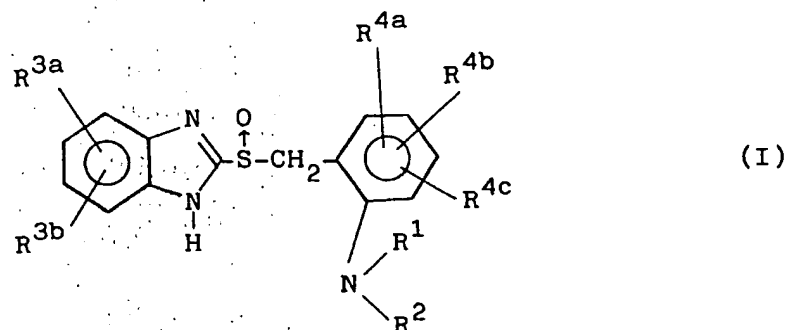
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**Description**

This invention relates to a stabilized benzimidazole derivative and a composition in which a benzimidazole derivative is stabilized.

**Description of prior art**

There is known a physiologically active benzimidazole derivative having the formula (I):



wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

The benzimidazole derivative of the formula (I) shows a prominent inhibitory action on secretion of gastric acid as is described in GB 2,161,160A and GB 2,163,747A (corresponding to DE 3,531,487A1). Moreover, some benzimidazole derivatives of the formula (I) can be employed as cytoprotective agents for gastrointestinal tract.

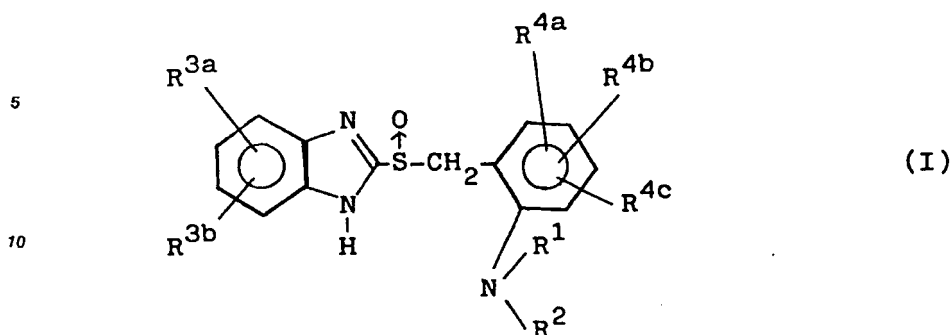
**SUMMARY OF THE INVENTION**

The present inventors have made study for actually utilizing the benzimidazole derivative of the formula (I) as a physiologically active component of a pharmaceutical and found that these benzimidazole derivative is poor in storage stability.

Accordingly, an object of the present invention is to provide a physiologically active benzimidazole derivative of the formula (I) which is improved in storage stability.

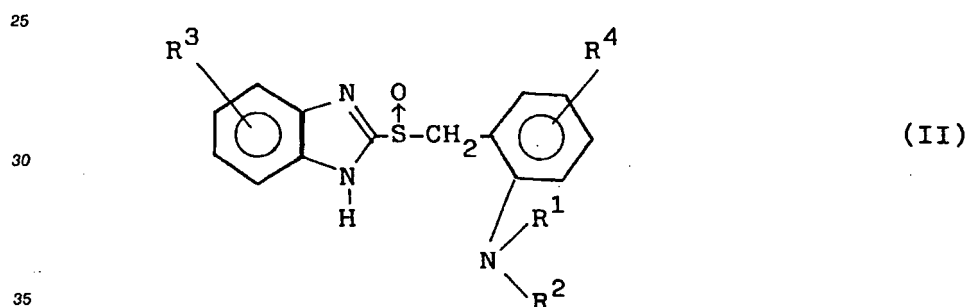
Another object of the invention is provide a composition containing a physiologically active benzimidazole derivative under stabilized condition.

There is provided by the present invention a physiologically active benzimidazole derivative having the formula (I):



15 wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen atom, a halogen atom, a fluoroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, which is in amorphous state or is kept in contact with an organic or inorganic basic material.

20 Particularly, the present invention provides a stabilized physiologically active benzimidazole derivative of the formula (II):



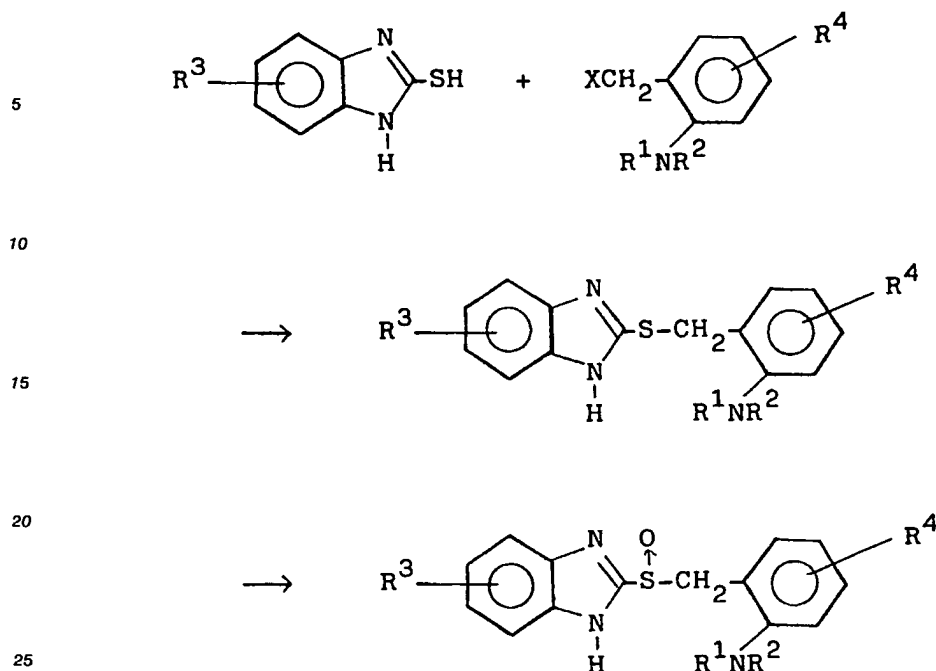
40 wherein R<sup>1</sup> is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R<sup>2</sup> is hydrogen atom or a lower alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a ring, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, which is in amorphous state or is kept in contact with an organic or inorganic basic material.

#### DETAILED DESCRIPTION OF THE INVENTION

45 The benzimidazole derivatives of the formula (I) can be prepared by known processes. For instance, the benzimidazole derivative of the formula (II) can be prepared by the process according to the following equation:

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wherein X is a reactive group and each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> has the same meaning as defined hereinbefore. The benzimidazole derivatives of the formula (I) other than the derivative of the formula (II) can be prepared in similar manners.

Representative examples of the compounds of the formula (I) include:

- Compound 1: 2-(2-dimethylaminobenzylsulfinyl)benzimidazole,
- Compound 2: 2-(2-diethylaminobenzylsulfinyl)benzimidazole,
- Compound 3: 2-(2-aminobenzylsulfinyl)benzimidazole,
- Compound 4: 2-(2-methylaminobenzylsulfinyl)benzimidazole,
- Compound 5: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxybenzimidazole,
- Compound 6: 2-(2-diethylaminobenzylsulfinyl)-5-methoxybenzimidazole,
- Compound 7: 2-(2-dimethylamino-6-methylbenzylsulfinyl)benzimidazole,
- Compound 8: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxycarbonylbenzimidazole,
- Compound 9: 2-(2-dimethylaminobenzylsulfinyl)-5-methylbenzimidazole,
- Compound 10: 5-chloro-2-(2-dimethylaminobenzylsulfinyl)benzimidazole,
- Compound 11: 5-amino-2-(2-dimethylaminobenzylsulfinyl)benzimidazole,
- Compound 12: 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole,
- Compound 13: 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole,
- Compound 14: 2-(2-piperidinobenzylsulfinyl)benzimidazole,
- Compound 15: 2-[2-(N-cyclohexyl-N-methylamino)benzylsulfinyl]benzimidazole, and
- Compound 16: 2-[2-(N-benzyl-N-methylamino)benzylsulfinyl]benzimidazole.

The benzimidazole derivative employed in the present invention preferably is a compound having the formula (I) wherein R<sup>1</sup> is an alkyl group containing 1-8 carbon atoms. R<sup>2</sup> preferably is a lower alkyl group. Preferably, each of R<sup>3a</sup> and R<sup>3b</sup> is independently hydrogen atom or an alkoxy group. Preferably, each of R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> is independently is hydrogen atom or a lower alkyl group. In the specification, the lower alkyl group and the lower alkoxy group mean those containing 1-6 carbon atoms.

As a result of the study of the present inventors, it has found that the benzimidazole derivative of the formula (I), which is prepared in the form of crystals according to known processes for the preparation, can be prominently improved in storage stability when it is formed in amorphous state.

The benzimidazole derivative of the formula (I) can be converted into a amorphous compound, for instance, by freezing a crystalline compound in an organic solvent and then evaporating the solvent. However, it is advantageous to treat the crystalline compound in such a manner that the crystalline

compound is dissolved in an organic solvent containing an organic polymer and then forcing to remove the solvent through evaporation or that the crystalline compound is dissolved in an organic solvent containing an organic polymer and then spray-drying the resulting solution.

In the above process, there is no need of dissolving the benzimidazole derivative and/or the organic polymer in the solvent. For instance, the benzimidazole derivative and/or organic polymer can be suspended in the organic solvent. For this reason, the organic solvent can be replaced with an aqueous organic solvent or replaced simply with water. In the case that water or an aqueous organic solvent is employed as the solvent, the organic polymer preferably is water-soluble. Further, in the case that water or an aqueous organic solvent is utilized, a surface active agent can be utilized as a dispersant.

Examples of the organic polymers employable for converting a crystalline benzimidazole derivative into an amorphous benzimidazole derivative include synthetic or natural polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch, agar and  $\alpha$ -cyclodextrin. Preferred are cellulose derivatives.

As described above, the organic polymer preferably is a water soluble polymer in the case the solvent is water or an aqueous organic solvent. Examples of the water-soluble polymers include carboxymethylcellulose sodium, poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch, and agar.

The organic polymer is preferably utilized in an amount of not less than 0.5 time, more preferably not less than 2 times as much as a weight of the benzimidazole derivative.

There is no limitation with respect to the organic solvent employed for the preparation of a solution of the benzimidazole derivative and the organic polymer, so long as the derivative and the polymer are dissolved in the solvent. Advantageously employable are alcohols and halogenated alkyls. As described above, the organic solvent can be used in combination with water and optionally with a surface active agent.

It is not known why the benzimidazole derivatives of the formula (I) are prominently improved in the storage stability by converting a crystalline product into an amorphous product. However, it can be thought as follows.

It is observed that the benzimidazole derivative of the formula (I) emits strong heat when it decomposes. Accordingly, it is assumed that when the benzimidazole derivative in crystalline state once starts decomposition locally at a certain area, decomposition is extended rapidly to other area by way of heat produced by the strong exothermic reaction. In amorphous state, the local decomposition of the benzimidazole derivative is extended slowly to other area because the produced heat is not transmitted to the surrounding area rapidly.

It is further assumed that the organic polymer introduced into the benzimidazole derivative composition serves for forcing the formation of an amorphous compound in the conversion procedure and further serves in the composition as a barrier between the resulting amorphous particles for suppressing transmission of heat from the decomposed area to other area, whereby further improving the storage stability of the benzimidazole derivative.

According to the present invention, the improvement of storage stability of the benzimidazole derivative of the formula (I) can be accomplished by bringing the derivative into contact with a basic material in an amount of not less than 5 weight %, preferably not less than 10 weight %, more preferably in the range of 10 to 200 weight %, based on an amount of the benzimidazole derivative. For instance, the contact between the benzimidazole derivative and the basic material can be attained by preparing a composition containing both the benzimidazole derivative and the basic material.

The basic material used herein means a material which shows pH 7 or higher, preferably pH 8 or higher, in the form of an aqueous solution or an aqueous suspension.

The basic material preferably is a hydroxide or a salt with a weak inorganic acid of a metal such as an alkali metal, an alkaline earth metal and aluminum. More concretely, the basic material preferably is a hydroxide such as alumina magnesium hydroxide ( $2.5\text{Al}_2\text{O}_3 \cdot \text{Mg}(\text{OH})_2$ ), aluminum hydroxide and magnesium hydroxide. Examples of the salts with a weak inorganic acid include carbonates such as potassium carbonate, calcium carbonate, sodium hydrogen carbonate and magnesium carbonate; phosphates such as potassium monohydrogen phosphate, potassium phosphate and sodium phosphate; and coprecipitation products of hydroxide with carbonate such as aluminum hydroxide-sodium hydrogen carbonate coprecipitation product and aluminum hydroxide-magnesium carbonate-calcium carbonate coprecipitation product.

The basic material may be a salt of an organic acid (e.g., higher fatty acid) with an alkali metal, an alkaline earth metal, aluminum and amine. The basic material may be an amide, a basic amino acid, a thiamine and an amine. Examples of the organic acids are fatty acids having 12-22 carbon atoms, benzoic

acid, alginic acid, edetic acid (EDTA), citric acid, glycyrrhizinic acid, glutamic acid, gluconic acid, succinic acid, fumaric acid, salicylic acid, and lactic acid. Preferred are higher fatty acids having 12-22 carbon atoms such as stearic acid, palmitic acid and myristic acid. Examples of the metals, include sodium, potassium, calcium, magnesium, and aluminum. Examples of the amines include isopropanolamine, diphenylamine, ethanolamine, and benzylamine.

Preferred salts of organic acids with an alkali metal, an alkaline earth metal and aluminum are sodium stearate, potassium stearate, magnesium stearate, aluminum stearate, sodium palmitate, potassium palmitate, magnesium palmitate, aluminum palmitate, sodium myristate, potassium myristate, magnesium myristate, aluminum myristate, sodium benzoate, sodium alginate, sodium edetate, sodium citrate, sodium glycyrrhizinate potassium glycyllcyinate, sodium glutamate, sodium gluconate, potassium gluconate, sodium succinate, sodium fumarate, sodium salicyate, and calcium lactate.

Examples of the amides include nicotinic amide and monomethylnicotinic amide. An example of the basic amino acid is histidine. An example of the thiamine is vitamin B<sub>1</sub>. Examples of the amines include diisopropanolamine, diphenylamine, ethanolamine and benzylamine.

In the composition containing both the benzimidazole derivative of the formula (I) and a basic material, the benzimidazole derivative preferably is present in the form of particles preferably having a mean diameter of not more than 10  $\mu$ m. The benzimidazole derivative of the formula (I) is more stable when it is in the form of such fine particles.

The benzimidazole derivative can be converted into fine particles using known micronizers for the preparation of fine particles. Examples of such micronizers include mechanical micronizers such as pin mill, attrition mill, screw crusher, ring roller mill, ball mill; and hydromechanical energy micronizers such as jet mill, jet pulverizer, micronizer, reductionizer jet pulverizer and air mill.

The stabilized amorphous benzimidazole derivative and the composition of the stabilized benzimidazole derivative shows prominent inhibitory action on secretion of gastric acid and also is employable as a cytoprotective agent for gastrointestinal tract. The stabilized benzimidazole derivative of the formula (I) and the composition containing the stabilized benzimidazole derivative can be administered orally or parenterally. Examples of the preparation forms for oral administration include tablets, capsules, powder, granules, and syrup. In the formulation of these preparations, there can be used excipients, disintegrants, binders, lubricants, pigments, diluents and the like which are commonly used in the art. Examples of the excipients include glucose, sucrose, lactose, and microcrystalline cellulose. Examples of the disintegrants include starch and carboxymethylcellulose calcium. Examples of the lubricants include hardened oil and talc. Examples of the binders include hydroxypropylcellulose, gelatin and polyvinylpyrrolidone. Other additives can be also used.

The dose is generally not more than 500 mg/day, preferably about 100  $\mu$ g/day to 300 mg/day, for an adult. This value is expressed in terms of the amount of the physiologically active compound, namely the benzimidazole derivative of the formula (I). The dose can be either increased or decreased depending upon the age and other conditions.

The present invention is further described by the following examples.

#### 40 Synthesis of 2-(2-Dimethylaminobenzylsulfanyl)benzimidazole

##### (1) 2-(2-Dimethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (4.73 g) was dissolved in 150 ml of ethanol, and to the solution was added 45 6.18 g of 2-dimethylaminobenzyl chloride hydrochloride. The mixture was stirred at room temperature for 30 minutes. Precipitated crystals were collected by filtration. A saturated aqueous NaHCO<sub>3</sub> solution was added to the crystals, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from a mixture of chloroform and acetonitrile to obtain 50 5.39 g of 2-(2-dimethylaminobenzylthio)benzimidazole as a colorless crystalline product (m.p. 164 °C).

##### (2) 2-(2-Dimethylaminobenzylsulfanyl)benzimidazole

2-(2-Dimethylaminobenzylthio)benzimidazole (4.8 g) was dissolved in a mixture of 40 ml of chloroform 55 and 5 ml of methanol. After the solution was chilled to 0 °C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added portionwise. Ten minutes later, a saturated aqueous NaHCO<sub>3</sub> solution was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The chloroform solution was washed with saturated brine and then dried over anhydrous sodium sulfate. The chloroform was distilled off

under reduced pressure and the residue was recrystallized from a mixture of chloroform and ether to obtain 2.97 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as a colorless crystalline product (m.p. 116°C, decomposed).

5 Example 1

In 10 ml of methyl alcohol were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)-benzimidazole and 3.0 g of hydroxypropylcellulose. The resulting solution was placed in a rotary evaporator for concentration. The concentrated residue was poured in a Petri dish, and placed overnight in a vacuum  
10 dryer at 35°C. The dried composition product was in the form of a pale yellow film.

The composition in the form of a film was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

15 Example 2

In 100 ml of chloroform were dissolved 3.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)-benzimidazole and 9.0 g of poly(vinylpyrrolidone). The resulting solution was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 3.5 ml/min. and a  
20 temperature of supplied air at 100°C, to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

25 Example 3

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed.  
30 Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 4

35 The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

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Example 5

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of methylcellulose to obtain a fine powdery composition.

45 The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 6

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In 30 ml of methylene chloride were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)-benzimidazole and 1.0 g of a nonionic surface active agent (low HLB type) to obtain an oily solution. Independently, in 250 ml of water were dissolved 3.0 g of carboxymethylcellulose sodium and 1.0 g of a nonionic surface active agent (high HLB type) to obtain an aqueous solution.

55 The oily solution and the aqueous solution were combined and violently mixed to give an emulsion. The resulting emulsion was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 2.0 ml/min. and a temperature of supplied air at 120°C, to obtain a fine powdery composition.



The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

5 Comparison Example 1

In a mortar were mixed 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole and 3.0 g of hydroxypropylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed.  
10 Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in crystalline state.

Comparison Example 2

15 The procedure of Comparison Example 1 was repeated except for replacing the hydroxypropylcellulose with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in crystalline state.

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Evaluation on Storage Stability

The 2-(2-dimethylaminobenzylsulfinyl)benzimidazole-containing compositions obtained in Examples were stored in a thermostat at 70°C for 6 days. In the course of the storage, an amount of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole remaining in the composition (i.e., remaining amount) was  
25 determined at lapse of 2 days, 4 days, and 6 days, to evaluate storage stability of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

The remaining amount of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was determined by taking out approx. 900 mg of the stored sample, weighing the taken sample, adding methanol to the sample to make a  
30 total volume of precisely 100 ml under shaking for extraction by methanol, diluting the methanolic extract to make a total volume of 100 times as much as the methanolic extract, subjecting 20  $\mu$ l of the diluted solution to determination based on HPLC (high pressure liquid chromatography) method.

The results are set forth in Table 1. The numerals in Table 1 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

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Table 1

Sample	Period of Storage			
	0 day	2 days	4 days	6 days
Example 1	100	98.2	96.6	86.6
Example 2	100	99.8	99.4	95.5
Example 3	100	99.5	98.8	99.2
Example 4	100	96.2	93.6	79.0
Example 5	100	95.5	90.0	85.3
Example 6	100	98.9	97.3	95.4
Com. Ex. 1	100	94.8	87.2	56.2
Com. Ex. 2	100	94.1	82.5	44.1

#### Examples 7 - 14

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm<sup>2</sup> and rate of 1 kg/hr to obtain a white microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (decomposition point: 121-127 °C, mean diameter 2 μm) in 95 % yield.

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was mixed with a basic material set forth in Table 2 at weight ratio of 1 : 1. The resulting composition was stored at 50 °C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfinyl) benzimidazole was determined in the same manner described above.

The results are set forth in Table 2.

#### Comparison Example 3

The procedure of Example 7 was repeated except that no basic material was mixed, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

#### Comparison Examples 4 - 11

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 2, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

Table 2

Sample	Added Material	Remaining amount (%)
Example 7	Alumina magnesium hydroxide	88.1
Example 8	Sodium carbonate	94.7
Example 9	Calcium hydrogen phosphate	95.8
Example 10	Aluminum hydroxide	80.8
Example 11	Magnesium methasilicate aluminate	51.1
Example 12	Anhydrous calcium phosphate	97.4
Example 13	Magnesium carbonate	78.9
Example 14	Sodium hydrogen carbonate	81.2
Com. Ex. 3	-----	1.7
Com. Ex. 4	Calcium sulfate	4.1
Com. Ex. 5	Lactose	0.8
Com. Ex. 6	D-Mannitol	0.9
Com. Ex. 7	Microcrystalline cellulose	10.5
Com. Ex. 8	Corn starch	3.0
Com. Ex. 9	Polyethylene glycol	1.0
Com. Ex. 10	Methylcellulose	1.4
Com. Ex. 11	Succinic acid	0.0

Remarks: The numerals in Table 2 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

#### Examples 15 - 17

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 3 and the storage period was changed to 30 days, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The results are set forth in Table 3.

Table 3

Sample	Added Material	Remaining amount (%)
Example 15	Alumina magnesium hydroxide	51.6
Example 16	Aluminum hydroxide	37.3
Example 17	Magnesium carbonate	55.0

Remarks: The numerals in Table 3 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 18 & 19 and Comparison Examples 12 - 13

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole prepared in Example 7 was mixed with additives set forth in Table 4 to obtain a 2-(2-dimethylaminobenzylsulfinyl)benzimidazole-containing composition.

Table 4

	Example		Comparison Example 12
	18	19	
Benzimidazole derivative	30	30	30
Lactose	47	37	57
Corn starch	10	10	10
Alumina magnesium hydroxide	10	20	-
Hydroxypropylcellulose	3	3	3

In Table 4, the numerals are expressed in terms of weight parts.

The resulting compositions and an untreated microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (for Comparison Example 13) were kept at 50 °C, 75%RH for 5 days, 10 days and 20 days, for evaluating storage stability in the same manner as described above.

The results are set forth in Table 5. The numerals in Table 5 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Table 5

Sample	Period of Storage			
	0 day	5 days	10 days	20 days
Example 18	100	99.6	95.2	93.4
Example 19	100	99.6	94.8	92.9
Com. Ex. 12	100	99.7	95.6	66.0
Com. Ex. 13	100	95.1	1.6	-

## Examples 20 - 22

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm<sup>2</sup> and rate of 1 kg/hr to obtain a white microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (decomposition point: 121-127 °C, mean diameter 2 μm) in 95 % yield.

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was mixed with a basic material set forth in Table 6 at weight ratio of 1 : 1. The resulting composition was stored at 50 °C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was determined in the same manner described above.

The results are set forth in Table 6.

Table 6

Sample	Added Material	Remaining amount (%)
Example 20	Nicotinamide	64.6
Example 21	Magnesium stearate	63.3
Example 22	Calcium stearate	35.8

Remarks: The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 23 & 24

The procedure of Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)-benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Example 23) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Example 24) and the amount of hydroxy propyl cellulose was changed into 5.0 g., to obtain an amorphous product. The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 and 8.

Examples 25 & 26

The procedure of Example 7 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)-benzimidazole was replaced with 2-(dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Example 25) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Example 26). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Examples 27 & 28

The procedure of Example 21 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)-benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Example 27) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Example 28). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 14 & 15

The procedure of Comparison Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Comparison Example 14) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Comparison Example 15). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 16 & 17

The procedure of Comparison Example 5 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Comparison Example 16) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Comparison Example 17). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 18 & 19

The procedure of Comparison Example 11 was repeated except that the 2-(2-dimethylaminobenzylsulfanyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfanyl)benzimidazole (for Comparison Example 18) and 2-(2-dimethylamino-5-methylbenzylsulfanyl)benzimidazole (for Comparison Example 19). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60 °C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Table 7  
[2-(2-dimethylamino-5-methoxybenzyl)sulfinylbenzimidazole]

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Sample	Storage Period		
	0 day	5 days	10 days
Example 23	100	99.8	99.5
Example 25	100	99.2	95.9
Example 27	100	99.6	96.9
Com. Ex. 14	100	98.3	74.6
Com. Ex. 16	100	99.2	78.1
Com. Ex. 18	100	0	-
Ref. Ex. 1	100	99.4	76.3

Remarks: Sample of Ref. Ex. 1 is an untreated microcrystalline 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.

The numerals in Table 7 mean relative amounts of the remaining 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.

Table 8  
[2-(2-dimethylamino-5-methylbenzyl)sulfinylbenzimidazole]

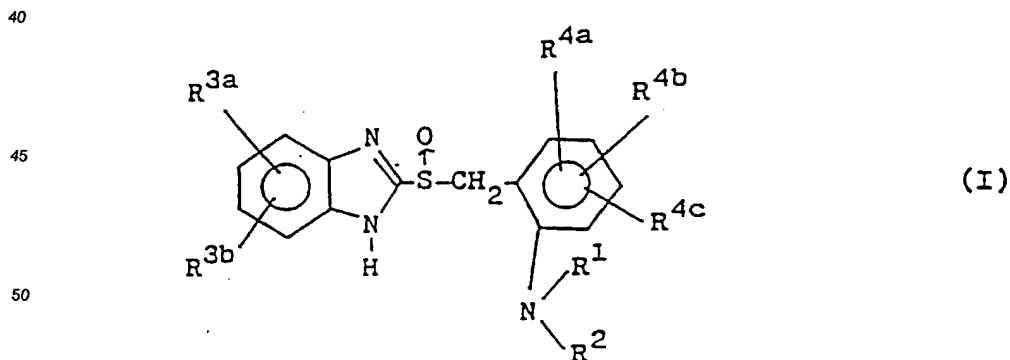
Sample	Storage Period		
	0 day	5 days	10 days
Example 24	100	99.2	99.2
Example 26	100	75.4	49.5
Example 28	100	87.5	71.8
Com. Ex. 15	100	9.9	4.5
Com. Ex. 17	100	60.1	0.1
Com. Ex. 19	100	0	-
Ref. Ex. 2	100	30.4	10.0

Remarks: Sample of Ref. Ex. 2 is an untreated microcrystalline 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.  
The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.

### Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, SE

1. A physiologically active benzimidazole derivative having the formula (I):

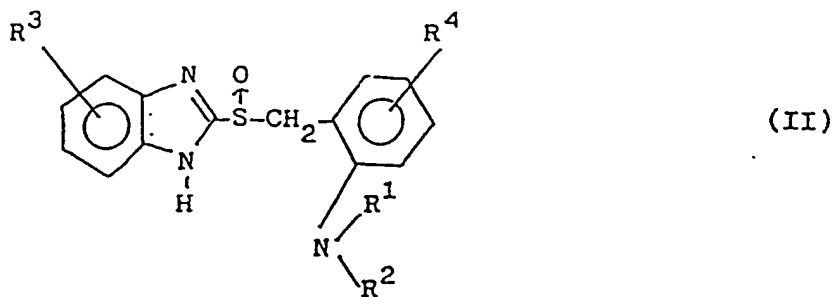


wherein R<sup>1</sup> is hydrogen, an alkyl group having from 1 to 8 carbon atoms, a fluoroalkyl group having from 1 to 6 carbon atoms, cyclohexyl, a phenyl group or benzyl, R<sup>2</sup> is hydrogen or an alkyl group having from 1 to 6 carbon atoms provided that when R<sup>1</sup> is cyclohexyl or benzyl, R<sup>2</sup> is methyl, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a piperidino group, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and



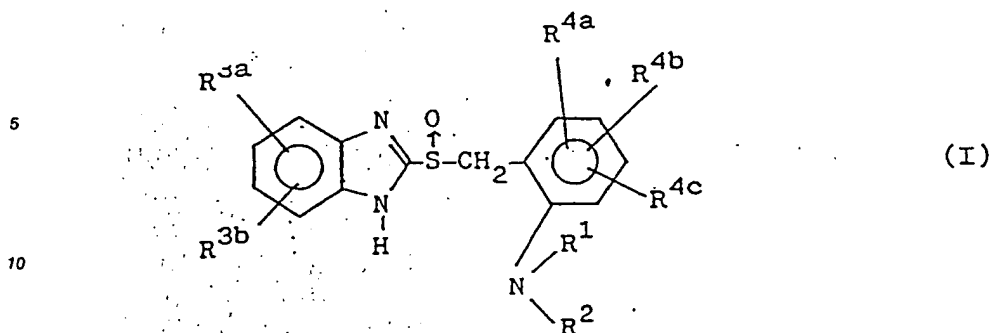
R<sup>4c</sup> independently is hydrogen, halogen, a fluoroalkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an alkoxycarbonyl group wherein the alkyl moiety has from 1 to 6 carbon atoms or an amino group, characterised in that the derivative is in the amorphous state and shows no diffraction pattern in X-ray diffraction analysis.

2. The benzimidazole derivative as claimed in claim 1, wherein the benzimidazole derivative has the formula (II):



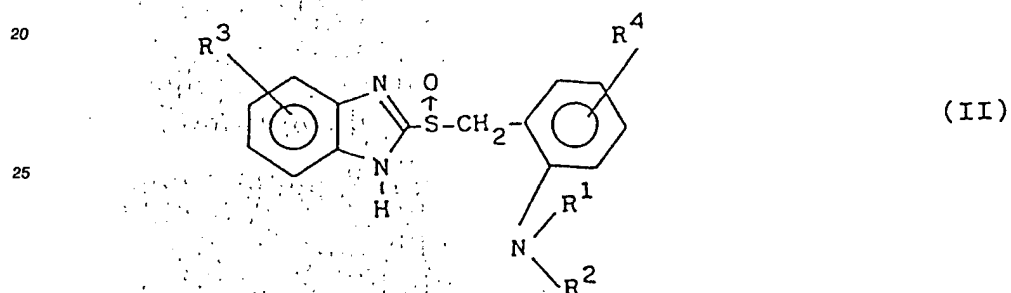
wherein R<sup>1</sup> is hydrogen, an alkyl group having from 1 to 8 carbon atoms, a cyclohexyl, a phenyl group or benzyl, R<sup>2</sup> is hydrogen or an alkyl group having from 1 to 6 carbon atoms, provided that where R<sup>1</sup> is cyclohexyl or benzyl, R<sup>2</sup> is methyl, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a piperidino group, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen, a halogen, trifluoromethyl group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an alkoxycarbonyl group wherein the alkyl moiety has from 1 to 6 carbon atoms or an amino group.

3. The benzimidazole derivative as claimed in claim 1, wherein R<sup>1</sup> of the formula (I) representing the benzimidazole derivative is an alkyl group having from 1 to 8 carbon atoms.
4. The benzimidazole derivative as claimed in claim 1, wherein R<sup>2</sup> of the formula (I) representing the benzimidazole derivative is an alkyl group having from 1 to 6 carbon atoms.
5. The benzimidazole derivative as claimed in claim 1, wherein each of R<sup>3a</sup> and R<sup>3b</sup> of the formula (I) representing the benzimidazole derivative is hydrogen or a lower alkoxy group having from 1 to 6 carbon atoms.
6. The benzimidazole derivative as claimed in claim 1, wherein each of R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> of the formula (I) representing the benzimidazole derivative is hydrogen or a lower alkyl group having from 1 to 6 carbon atoms.
7. A composition containing a physiologically active amorphous benzimidazole derivative having the formula (I):



15 wherein the R groups have the meanings as defined in claim 1, dispersed in an organic polymer.

8. The composition as claimed in claim 7, wherein the benzimidazole derivative has the formula (II):



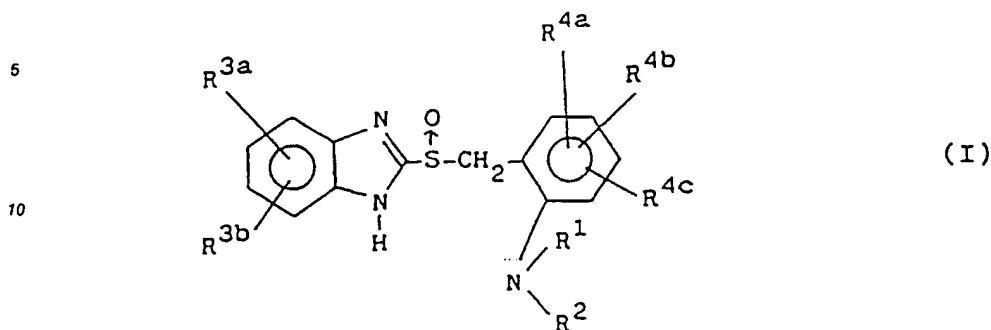
wherein the R groups have the meanings as defined in claim 2.

- 35 9. The composition as claimed in claim 7, wherein the organic polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch and agar.
- 40 10. The composition as claimed in claim 7, wherein the organic polymer is a cellulose derivative.
11. The composition as claimed in claim 7, wherein the organic polymer is a water soluble polymer.
- 45 12. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 0.5 time as much as a weight of the benzimidazole derivative.
13. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 2 times as much as a weight of the benzimidazole derivative.

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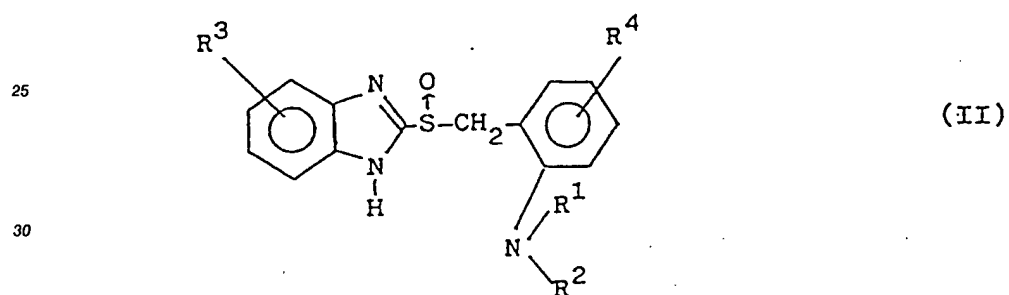
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14. A composition containing a physiologically active benzimidazole derivative having the formula (I):



wherein the R groups have the meanings as defined in claim 1, and a basic material in an amount of not less than 5 weight % based on an amount of the benzimidazole derivative.

20 15. The composition as claimed in claim 14, wherein the benzimidazole derivative has the formula (II):



35 wherein the R groups have the meanings as defined in claim 2.

16. The composition as claimed in claim 14, wherein the basic material is a hydroxide or a salt with a weak inorganic acid of a metal selected from the group consisting of an alkali metal, an alkaline earth metal and aluminum.

40 17. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of alumina magnesium hydroxide, aluminum hydroxide and magnesium carbonate.

45 18. The composition as claimed in claim 14, wherein the basic material is a salt of an organic acid with an alkali metal, an alkaline earth metal, aluminum and amine.

19. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of amide, basic amino acids, thiamines and amines.

50 20. The composition as claimed in claim 14, wherein the basic material is a salt of a higher fatty acid with an alkali metal or an alkaline earth metal.

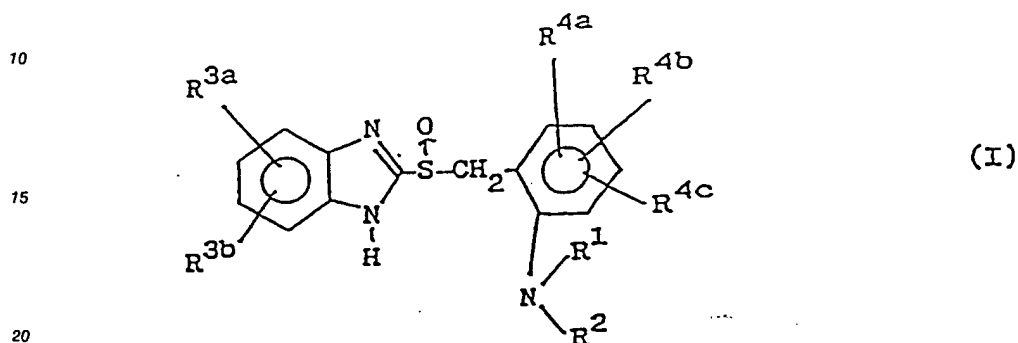
21. The composition as claimed in claim 14, wherein the basic material is contained in an amount of not less than 10 weight % based on an amount of the benzimidazole derivative.

55 22. The composition as claimed in claim 14, wherein the basic material is contained in an amount of 10 to 200 weight % based on an amount of the benzimidazole derivative.

23. The composition as claimed in claim 14, wherein the benzimidazole derivative is contained in the form of particles having a mean diameter of not more than 10  $\mu\text{m}$ .

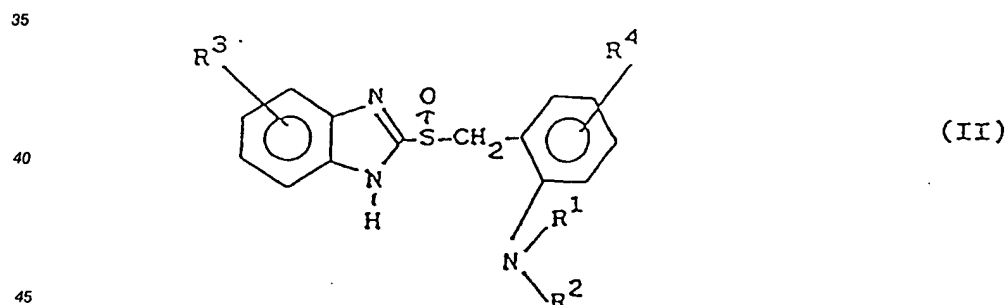
**Claims for the following Contracting State : ES**

1. A process for stabilizing a physiologically active benzimidazole derivative having the formula (I):



25 wherein R<sup>1</sup> is hydrogen, an alkyl group having from 1 to 8 carbon atoms, a fluoroalkyl group having from 1 to 6 carbon atoms, cyclohexyl, a phenyl group or a benzyl group, R<sup>2</sup> is hydrogen or an alkyl group having from 1 to 6 carbon atoms provided that when R<sup>1</sup> is cyclohexyl or benzyl, R<sup>2</sup> is methyl, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a piperidino group, and each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> independently is hydrogen, a halogen, a fluoroalkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an alkoxycarbonyl group wherein the alkyl moiety has from 1 to 6 carbon atoms or an amino group, characterised in that the process comprises converting the benzimidazole derivative of the formula (I) into an amorphous state.

2. A process according to claim 1, characterised in that the benzimidazole derivative has the formula (II):



50 wherein R<sup>1</sup> is hydrogen, an alkyl group having from 1 to 8 carbon atoms, a cyclohexyl, a phenyl group or a benzyl group, R<sup>2</sup> is hydrogen or an alkyl group having from 1 to 6 carbon atoms, provided that where R<sup>1</sup> is cyclohexyl or benzyl, R<sup>2</sup> is methyl, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent nitrogen atom form a piperidino group, and each of R<sup>3</sup> and R<sup>4</sup> independently is hydrogen, a halogen, a trifluoromethyl group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an alkoxycarbonyl group wherein the alkyl moiety has from 1 to 6 carbon atoms or an amino group.

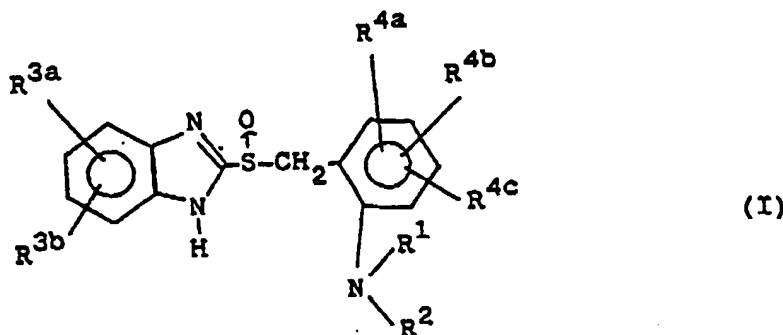
- 55 3. A process according to claim 1 or claim 2, the process comprising dispersing the benzimidazole derivative of the formula (I) or (II) in an organic polymer.

4. A process according to claim 3, characterised in that the organic polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly (sodium acrylate), sodium alginate, gelatin, gum arabic,  $\alpha$ -starch, oxidized starch, heat-treated starch, enzyme-treated starch and agar.
5. A process according to claim 1 or claim 2, the process comprising mixing the benzimidazole derivative of the formula (I) or (II) with a basic material in an amount of not less than 5% by weight based on the benzimidazole derivative.
6. A process according to claim 5, characterised in that the basic material is a hydroxide or a weak inorganic acid salt of a metal selected from the group consisting of an alkali metal, an alkaline earth metal and aluminium.
7. A process according to claim 5, characterised in that the basic material is selected from the group consisting of alumina magnesium hydroxide, aluminium hydroxide and magnesium carbonate.
8. A process according to claim 5, characterised in that the basic material is a salt of an organic acid with an alkali metal, an alkaline earth metal, aluminium and amine.
9. A process according to claim 5, characterised in that the basic material is selected from the group consisting of amides, basic amino acids, thiamines and amines.
10. A process according to claim 5, characterised in that the basic material is a higher fatty acid salt of an alkali metal or an alkaline earth metal.
11. A process according to any of claims 5 to 10, characterised in that the basic material is contained in an amount of not less than 10% by weight based on the benzimidazole derivative.
12. A process according to claim 11, characterised in that the basic material is contained in an amount of 10 to 200% by weight, based on the benzimidazole derivative.
13. A process according to any of claims 5 to 12, characterised in that the benzimidazole derivative is in the form of particles having a mean diameter of not more than 10  $\mu\text{m}$ .

#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

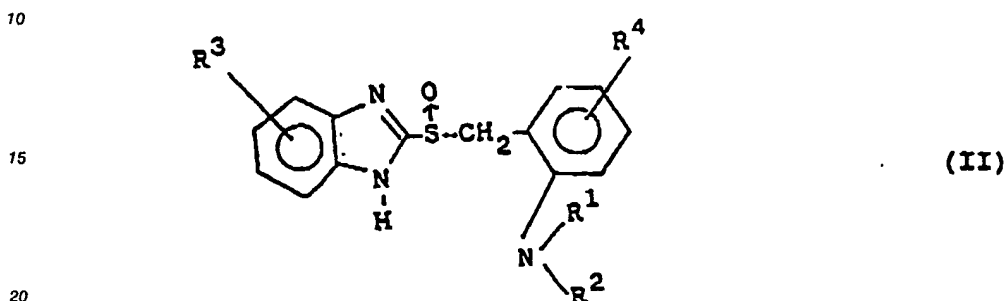
1. Physiologisch aktives Benzimidazolderivat der Formel (I):



in der R<sup>1</sup> Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Fluoralkylgruppe mit 1 bis 6 Kohlenstoffatomen, Cyclohexyl, eine Phenylgruppe oder Benzyl, R<sup>2</sup> Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen sind, oder wobei R<sup>1</sup> und R<sup>2</sup> zusammen mit dem benachbarten

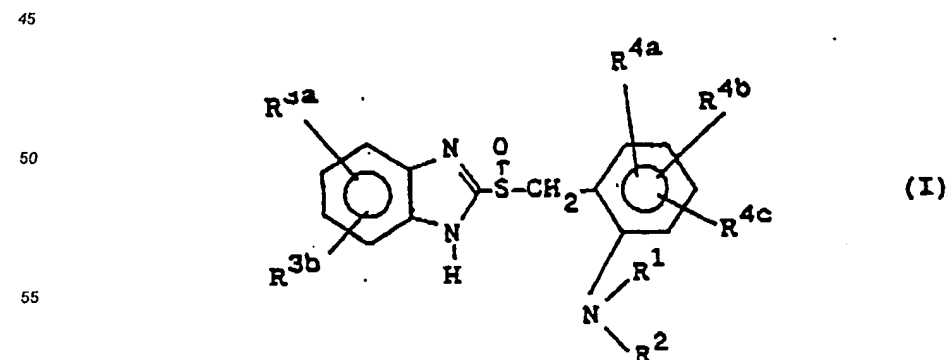
Stockstoffatom einen Ring bilden, und  $R^{3a}$ ,  $R^{3b}$ ,  $R^{4a}$ ,  $R^{4b}$  und  $R^{4c}$  jeweils unabhängig voneinander Wasserstoff, Halogen, eine Fluoralkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxycarbonylgruppe, in der der Alkylteil 1 bis 6 Kohlenstoffatome aufweist, oder eine Aminogruppe sind, dadurch gekennzeichnet, daß das Derivat in amorphem Zustand vorliegt und bei der Röntgenstrahl-Streuungsanalyse kein Beugungsmuster oder Beugungsbild ergibt.

2. Benzimidazolderivat nach Anspruch 1, wobei das Benzimidazolderivat die Formel (II) aufweist:



25 wobei  $R^1$  Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, Cyclohexyl, eine Phenylgruppe oder Benzyl,  $R^2$  Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen sind, oder wobei  $R^1$  und  $R^2$  zusammen mit dem benachbarten Stickstoffatom einen Ring bilden, und wobei  $R^3$  und  $R^4$  unabhängig voneinander Wasserstoff, Halogen, eine Trifluormethylgruppe, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxycarbonylgruppe, in der der Alkylteil 1 bis 6 Kohlenstoffatome aufweist, oder eine Aminogruppe sind.

- 30 3. Benzimidazolderivat nach Anspruch 1, wobei  $R^1$  in der Formel (I) den Benzimidazolderivats eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen ist.
- 35 4. Benzimidazolderivat nach Anspruch 1, wobei  $R^2$  der Formel (I) des Benzimidazolderivats eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist.
5. Benzimidazolderivat nach Anspruch 1, wobei  $R^{3a}$  und  $R^{3b}$  der Formel (I) des Benzimidazolderivats Wasserstoff oder eine niedere Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist.
- 40 6. Benzimidazolderivat nach Anspruch 1, wobei  $R^{4a}$ ,  $R^{4b}$  und  $R^{4c}$  der Formel (I) des Benzimidazolderivats Wasserstoff oder eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen sind.
7. Zusammensetzung mit Gehalt an einem physiologisch aktiven amorphen Benzimidazolderivat der Formel (I)



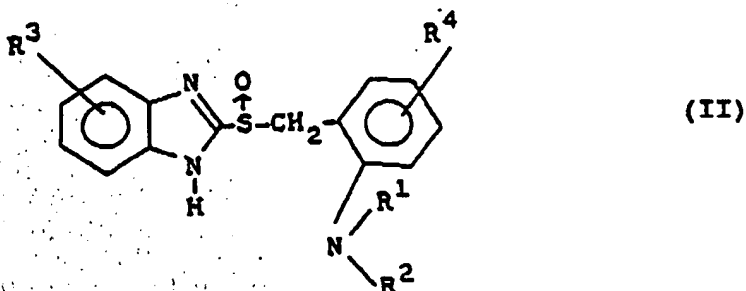
wobei die R-Gruppen die in Anspruch 1 wiedergegebene Bedeutung besitzen, das in einem organischen Polymer dispergiert ist.

8. Zusammensetzung nach Anspruch 7, wobei das Benzimidazolderivat die Formel (II) aufweist:

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wobei die R-Gruppen die Bedeutung gemäß Anspruch 2 besitzen.

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9. Zusammensetzung nach Anspruch 7, wobei das organische Polymer Hydroxypropylzellulose, Hydroxypropylmethylzellulose, Methylzellulose, Ethylzellulose, Carboxymethylzellulose-Natrium, Poly(vinylpyrrolidon), Poly(vinylalkohol), Poly(natriumacrylat), Natriumalginat, Gelatine, Gumarabicum,  $\alpha$ -Stärke, oxidierte Stärke, hitzebehandelte Stärke, enzymbehandelte Stärke und/oder Agar ist.

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10. Zusammensetzung nach Anspruch 7, wobei das organische Polymer ein Zellulosederivat ist.

11. Zusammensetzung nach Anspruch 7, wobei das organische Polymer ein wasserlösliches Polymer ist.

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12. Zusammensetzung nach Anspruch 7, wobei das organische Polymer in Mengen von nicht weniger als 0,5 mal das Gewicht des Benzimidazolderivats enthalten ist.

13. Zusammensetzung nach Anspruch 7, wobei das organische Polymer in Mengen von nicht weniger als 2 mal das Gewicht des Benzimidazolderivats enthalten ist.

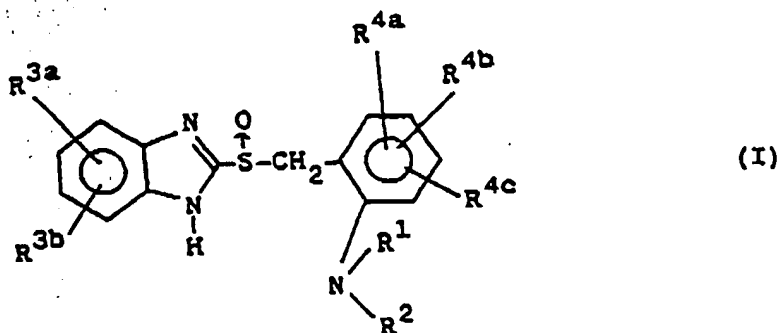
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14. Zusammensetzung mit Gehalt an einem physiologisch aktiven Benzimidazolderivat der Formel (I):

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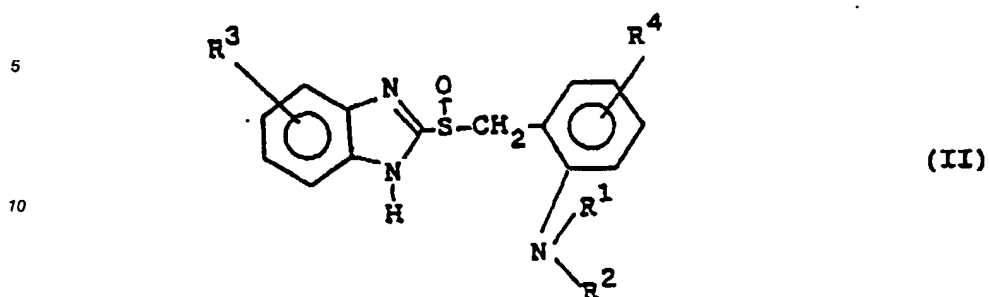
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wobei die R-Gruppen die Bedeutung gemäß Anspruch 1 haben, und einem basischen Material in Mengen von nicht weniger als 5 Gew.-%, bezogen auf die Menge Benzimidazolderivat.

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15. Zusammensetzung nach Anspruch 14, wobei das Benzimidazolderivat der Formel (II) entspricht:



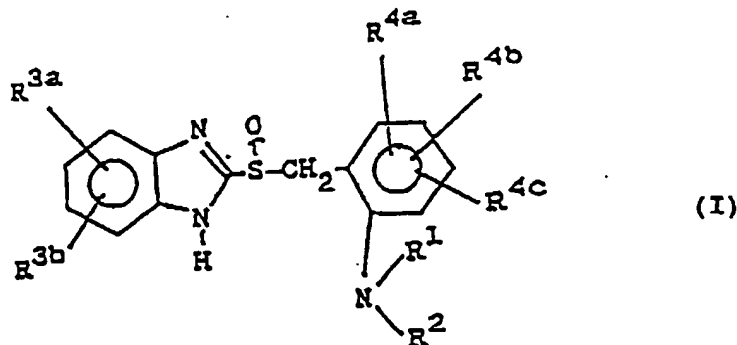
15 wobei die R-Gruppen die Bedeutung gemäß Anspruch 2 besitzen.

16. Zusammensetzung nach Anspruch 14, wobei das basische Material ein Hydroxid oder ein Salz eines Alkali-, eines Erdalkalimetalls und/oder Aluminiums mit einer schwachen anorganischen Säure ist.
17. Zusammensetzung nach Anspruch 14, wobei das basische Material Aluminiummagnesiumhydroxid, Aluminiumhydroxid und/oder Magnesiumcarbonat ist.
18. Zusammensetzung nach Anspruch 14, wobei das basische Material ein Salz einer organischen Säure mit einem Alkalimetall, einem Erdalkalimetall, Aluminium und/oder Amin ist.
19. Zusammensetzung nach Anspruch 14, wobei das basische Material ein Amid, basische Aminosäuren, Thiamine und/oder Amine sind.
20. Zusammensetzung nach Anspruch 14, wobei das basische Material ein Salz einer höheren Fettsäure mit einem Alkalimetall und/oder einem Erdalkalimetall ist.
21. Zusammensetzung nach Anspruch 14, wobei das basische Material in Mengen von nicht weniger als 10 Gew.-%, bezogen auf die Menge Benzimidazolderivat, enthalten ist.
22. Zusammensetzung nach Anspruch 14, wobei das basische Material in Mengen von 10 bis 200 Gew.-%, bezogen auf die Menge des Benzimidazolderivats enthalten ist.
23. Zusammensetzung nach Anspruch 14, wobei das Benzimidazolderivat in Form Von Partikeln eines mittleren Durchmessers von nicht mehr als 10  $\mu\text{m}$  enthalten ist.



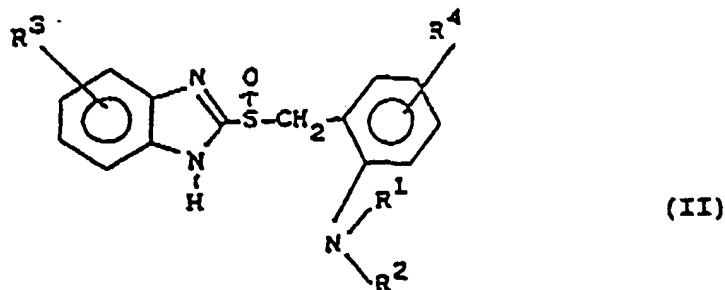
## Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zum Stabilisieren eines physiologisch aktiven Benzimidazolderivats der Formel (I):



wobei R<sup>1</sup> Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Fluoralkylgruppe mit 1 bis 6 Kohlenstoffatomen, Cyclohexyl, eine Phenylgruppe oder eine Benzylgruppe, R<sup>2</sup> Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen sind, vorausgesetzt, daß, wenn R<sup>1</sup> Cyclohexyl oder Benzyl, R<sup>2</sup> Methyl ist, oder wobei R<sup>1</sup> und R<sup>2</sup> zusammen mit dem benachbarten Stickstoffatom eine Piperidino-  
gruppe bilden, und wobei R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> und R<sup>4c</sup> unabhängig voneinander Wasserstoff, Halogen, eine Fluoralkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxycarbonylgruppe, in der der Alkylanteil 1 bis 6 Kohlenstoffatome aufweist, oder eine Aminogruppe sind, dadurch gekennzeichnet, daß bei dem Verfahren das Benzimidazolderivat der Formel (I) in einen amorphen Zustand überführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Benzimidazolderivat der Formel (II) entspricht:



in der R<sup>1</sup> Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, Cyclohexyl, eine Phenylgruppe oder eine Benzylgruppe, R<sup>2</sup> Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen sind, vorausgesetzt, daß, wenn R<sup>1</sup> Cyclohexyl oder Benzyl ist, R<sup>2</sup> Methyl ist, oder wobei R<sup>1</sup> und R<sup>2</sup> zusammen mit dem benachbarten Stickstoffatom eine Piperidinogruppe bilden, und wobei R<sup>3</sup> und R<sup>4</sup> unabhängig voneinander Wasserstoff, Halogen, Trifluormethylgruppe, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkoxycarbonylgruppe, in der der Alkylanteil von 1 bis 6 Kohlenstoffatomen aufweist, und/oder eine Aminogruppe sind.

3. Verfahren nach Anspruch 1 oder 2, wobei das Benzimidazolderivat der Formel (I) oder (II) in einem organischen Polymer dispergiert ist.
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß das organische Polymer Hydroxypropylzello-  
lose, Hydroxypropylmethylzello-lose, Methylzello-lose, Ethylzello-lose, Carboxymethylzello-lose-Natrium,

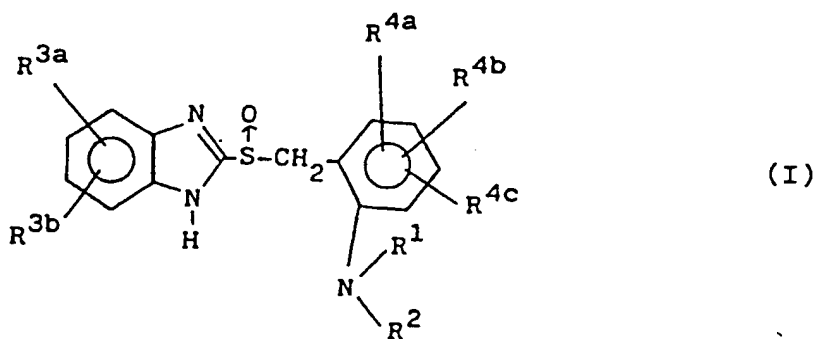
Poly(vinylpyrrolidon), Poly(vinylalkohol), Poly(natriumacrylat), Natriumalginat, Gelatine, Gumarabicum,  $\alpha$ -Stärke, oxidierte Stärke, hitzebehandelte Stärke, enzymbehandelte Stärke und/oder Agar ist.

- 5 5. Verfahren nach Anspruch 1 oder 2, bei dem das Benzimidazolderivat gemäß Formeln (I) oder (II) mit einem basischen Material in Mengen von nicht Weniger als 5 Gew.-%, bezogen auf das Benzimidazolderivat, vermischt wird.
- 10 6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das basische Material ein Hydroxid oder ein schwaches anorganischen Säuresalz eines Alkalimetalls, eines Erdalkalimetalls und/oder Aluminiums ist.
7. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das basische Material Aluminiummagnesiumhydroxid, Aluminiumhydroxid und/oder Magnesiumcarbonat ist.
- 15 8. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das basische Material ein Salz einer organischen Säure mit einem Alkalimetall, einem Erdalkalimetall, Aluminium und/oder Amin ist.
9. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das basische Material Amide, basische Aminosäuren, Thiamine und/oder Amine ist.
- 20 10. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das basische Material ein höheres Fettsäuresalz eines Alkali- oder Erdalkalimetalls ist.
11. Verfahren nach einem der Ansprüche 5 bis 10, dadurch gekennzeichnet, daß das basische Material in Mengen von nicht weniger als 10 Gew.-%, bezogen auf das Benzimidazolderivat, enthalten ist.
- 25 12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß das basische Material in Mengen von 10 bis 200 Gew.-%, bezogen auf das Benzimidazolderivat, enthalten ist.
- 30 13. Verfahren nach einem der Ansprüche 5 bis 12, dadurch gekennzeichnet, daß das Benzimidazolderivat in Form von Partikeln eines mittleren Durchmessers von nicht mehr als 10  $\mu\text{m}$  vorliegt.

# Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE

- 35 1. Dérivé de benzimidazole physiologiquement actif ayant la formule (I) :



40 dans laquelle R<sup>1</sup> est l'hydrogène, un groupe alkyle ayant de 1 à 8 atomes de carbone, un groupe fluoroalkyle ayant de 1 à 6 atomes de carbone, cyclohexyle, un groupe phényle ou benzyle, R<sup>2</sup> est l'hydrogène ou un groupe alkyle ayant de 1 à 6 atomes de carbone, ou R<sup>1</sup> et R<sup>2</sup> conjointement avec l'atome d'azote contigu forment un cycle, et chacun de R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> et R<sup>4c</sup> indépendamment est l'hydrogène, l'halogène, un groupe fluoroalkyle ayant de 1 à 6 atomes de carbone, un groupe alkyle ayant de 1 à 6 atomes de carbone, un groupe alcoxy ayant de 1 à 6 atomes de carbone, un groupe alcoxycarbonyl dans lequel la partie alkyle a de 1 à 6 atomes de carbone ou un groupe amino,

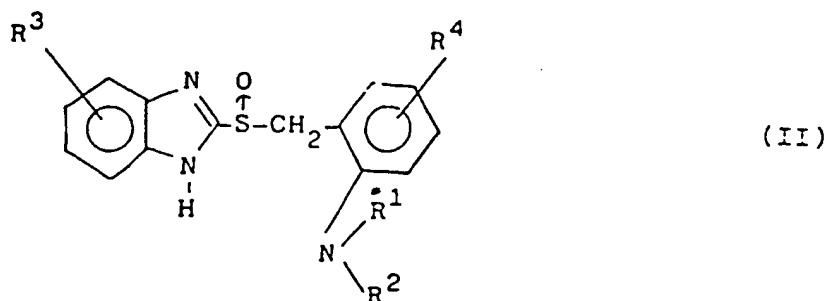
caractérisé en ce que le dérivé est dans l'état amorphe et ne présente aucun indice de diffraction dans l'analyse de diffraction aux rayons X.

2. Dérivé de benzimidazole selon la revendication 1, dans lequel le dérivé benzimidazole a la formule (II) :

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20 dans laquelle R<sup>1</sup> est l'hydrogène, un groupe alkyle ayant de 1 à 8 atomes de carbone, un cyclohexyle, un groupe phényle ou benzyle, R<sup>2</sup> est l'hydrogène ou un groupe alkyle ayant de 1 à 6 atomes de carbone, ou R<sup>1</sup> et R<sup>2</sup> conjointement avec l'atome d'azote contigu forment un cycle, et chacun de R<sup>3</sup>, et R<sup>4</sup> indépendamment est l'hydrogène, un halogène, un groupe trifluorométhyle, un groupe alkyle ayant de 1 à 6 atomes de carbone, un groupe alcoxy ayant de 1 à 6 atomes de carbone, un groupe

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3. Dérivé de benzimidazole selon la revendication 1, dans lequel R<sup>1</sup> de la formule (I) représentant le dérivé de benzimidazole est un groupe alkyle ayant de 1 à 8 atomes de carbone.

4. Dérivé de benzimidazole selon la revendication 1, dans lequel R<sup>2</sup> de la formule (I) représentant le dérivé de benzimidazole est un groupe alkyle ayant de 1 à 6 atomes de carbone.

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5. Dérivé de benzimidazole selon la revendication 1, dans lequel chacun de R<sup>3a</sup> et R<sup>3b</sup> de la formule (I) représentant le dérivé de benzimidazole est l'hydrogène ou un groupe alcoxy inférieur ayant de 1 à 6 atomes de carbone.

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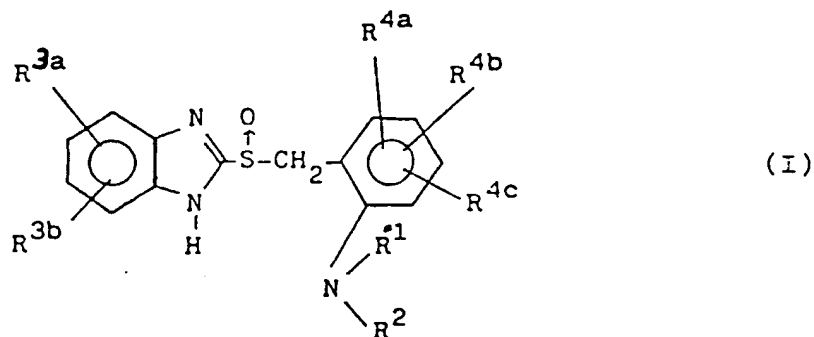
6. Dérivé de benzimidazole selon la revendication 1, dans lequel chacun de R<sup>4a</sup>, R<sup>4b</sup> et R<sup>4c</sup> de la formule (I) représentant le dérivé de benzimidazole est l'hydrogène ou un groupe alkyle inférieur ayant de 1 à 6 atomes de carbone.

- 40 7. Composition contenant un dérivé de benzimidazole amorphe actif physiologiquement ayant la formule (I) :

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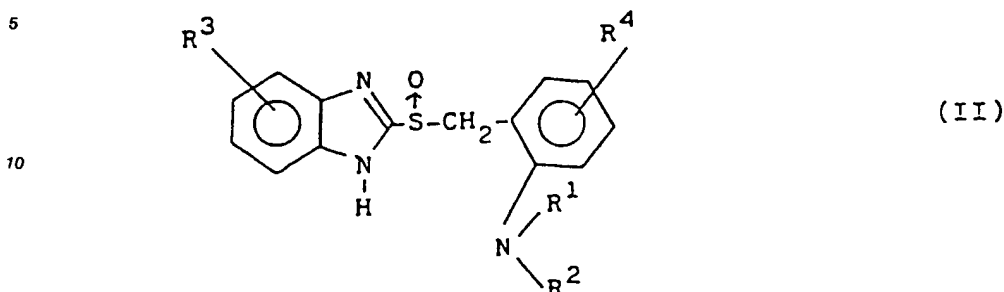
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dans laquelle les groupes R ont les significations définies dans la revendication 1 et sont mis en

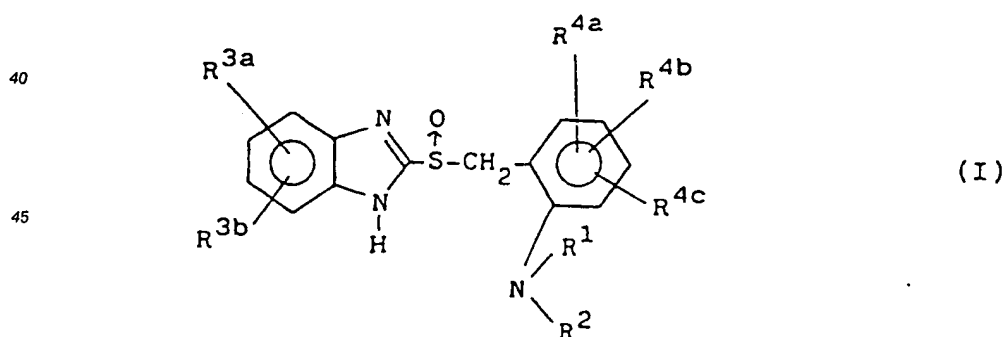
dispersion dans un polymère organique.

8. Composition selon la revendication 7, dans laquelle le dérivé de benzimidazole a la formule (II) :



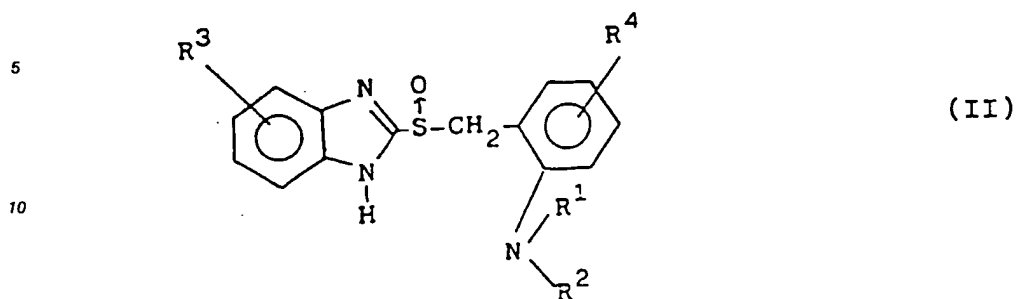
dans laquelle les groupes R ont les significations définies dans la revendication 2.

9. Composition selon la revendication 7, dans laquelle le polymère organique est choisi dans le groupe constitué par l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose, la méthylcellulose, l'éthylcellulose, le sodium de carboxyméthylcellulose, la poly(vinylpyrrolidone), un poly(vinylalcool), un poly(sodium acrylate), un alginat de sodium, la gélatine, de la gomme arabique, l' $\alpha$ -amidon, de l'amidon oxydé, de l'amidon traité à chaud, de l'amidon traité par enzyme et l'agar.
10. Composition selon la revendication 7, dans laquelle le polymère organique est un dérivé de cellulose.
11. Composition selon la revendication 7, dans laquelle le polymère organique est un polymère soluble dans l'eau.
12. Composition selon la revendication 7, dans laquelle le polymère organique est contenu dans une quantité non inférieure à 0,5 fois le poids du dérivé de benzimidazole.
13. Composition selon la revendication 7, dans laquelle le polymère organique est contenu dans une quantité non inférieure à 2 fois le poids du dérivé de benzimidazole.
14. Composition contenant un dérivé de benzimidazole actif physiologiquement ayant la formule (I) :



dans laquelle les groupes R ont les significations définies dans la revendication 1, et une matière de base dans une quantité non inférieure à 5 % en poids rapportés à la quantité du dérivé de benzimidazole.

15. Composition selon la revendication 14, dans laquelle le dérivé de benzimidazole a la formule (II) :



dans laquelle les groupes R ont les significations définies dans la revendication 2.

16. Composition selon la revendication 14, dans laquelle la matière de base est un hydroxyde ou un sel avec un acide inorganique faible d'un métal choisi dans le groupe constitué par un métal alcalin, un métal alcalino-terreux et l'aluminium.

17. Composition selon la revendication 14, dans laquelle la matière de base est choisie dans le groupe constitué par l'hydroxyde de magnésium d'alumine, l'hydroxyde d'aluminium et le carbonate de magnésium.

18. Composition selon la revendication 14, dans laquelle la matière de base est un sel d'un acide organique avec un métal alcalin, un métal alcalino-terreux, l'aluminium et une amine.

19. Composition selon la revendication 14, dans laquelle la matière de base est choisie dans le groupe constitué par un amide, des acides aminés basiques, des thiamines et des amines.

20. Composition selon la revendication 14, dans laquelle la matière de base est un sel d'un acide gras supérieur avec un métal alcalin ou un métal alcalino-terreux.

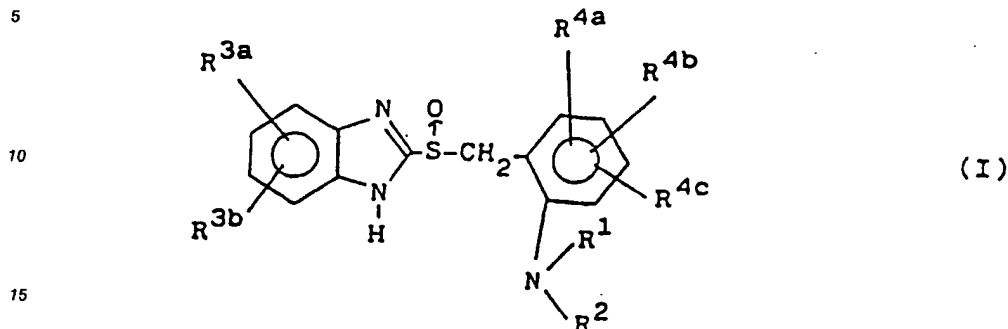
21. Composition selon la revendication 14, dans laquelle la matière de base est contenue dans une quantité non inférieure à 10 % en poids rapportés à la quantité du dérivé de benzimidazole.

22. Composition selon la revendication 14, dans laquelle la matière de base est contenue dans une quantité de 10 à 200 % en poids rapportés à la quantité du dérivé de benzimidazole.

23. Composition selon la revendication 14, dans laquelle le dérivé de benzimidazole est contenu sous forme de particules ayant un diamètre moyen non supérieur à 10 μm.

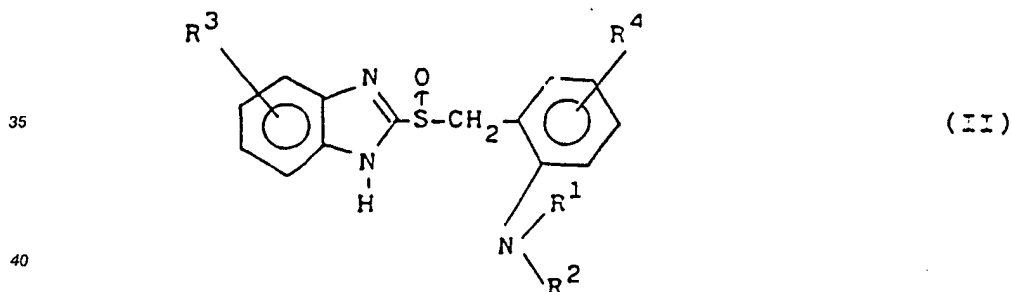
## Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la stabilisation d'un dérivé de benzimidazole physiologiquement actif ayant la formule (I):



20 dans laquelle R<sup>1</sup> est l'hydrogène, un groupe alkyle ayant de 1 à 8 atomes de carbone, un groupe fluoroalkyle ayant de 1 à 6 atomes de carbone, cyclohexyle, un groupe phényle ou un groupe benzyle, R<sup>2</sup> est l'hydrogène ou un groupe alkyle ayant de 1 à 6 atomes de carbone, dans la mesure où R<sup>1</sup> est cyclohexyle ou benzyle, R<sup>2</sup> est méthyle ou R<sup>1</sup> et R<sup>2</sup> conjointement avec l'atome d'azote contigu forment un groupe pipéridino, et chacun de R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4a</sup>, R<sup>4b</sup> et R<sup>4c</sup> indépendamment est l'hydrogène, un halogène, un groupe fluoroalkyle ayant de 1 à 6 atomes de carbone, un groupe alkyle ayant de 1 à 6 atomes de carbone, un groupe alcoxy ayant de 1 à 6 atomes de carbone, un groupe alcoxycarbonyle dans lequel l'élément alkyl a de 1 à 6 atomes de carbone ou un groupe amino, caractérisé en ce que le procédé comprend la conversion du dérivé de benzimidazole de la formule (I) dans un état amorphe.

2. Procédé selon la revendication 1, caractérisé en ce que le dérivé de benzimidazole a la formule (II) :



45 dans laquelle R<sup>1</sup> est l'hydrogène, un groupe alkyle ayant de 1 à 8 atomes de carbone, cyclohexyle, un groupe phényle ou un groupe benzyle, R<sup>2</sup> est l'hydrogène ou un groupe alkyle ayant de 1 à 6 atomes de carbone, dans la mesure où R<sup>1</sup> est cyclohexyle ou benzyle, R<sup>2</sup> est méthyle ou R<sup>1</sup> et R<sup>2</sup> conjointement avec l'atome d'azote contigu forment un groupe pipéridino, et chacun de R<sup>3</sup>, et R<sup>4</sup> indépendamment est l'hydrogène, un halogène, un groupe trifluorométhyle, un groupe alkyle ayant de 1 à 6 atomes de carbone, un groupe alcoxy ayant de 1 à 6 atomes de carbone, un groupe alcoxycarbonyle dans lequel l'élément alkyle a de 1 à 6 atomes de carbone ou un groupe amino.

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3. Procédé selon la revendication 1 ou la revendication 2, le procédé comprenant la mise en dispersion du dérivé de benzimidazole de la formule (I) ou (II) dans un polymère organique.
- 55 4. Procédé selon la revendication 3, caractérisé en ce que le polymère organique est choisi dans le groupe constitué par l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose, la méthylcellulose, l'éthylcellulose, le sodium de carboxyméthylcellulose, la poly(vinylpyrrolidone), le poly(vinylalcool), le poly(sodium acrylate), l'alginate de sodium, la gélatine, la gomme arabique, l' $\alpha$ -amidon, l'amidon oxydé,

l'amidon traité à chaud, l'agar et l'amidon traité par enzyme.

5. Procédé selon la revendication 1 ou la revendication 2, le procédé comprenant le mélange du dérivé de benzimidazole de la formule (I) ou (II) avec une matière de base dans une quantité non inférieure à 5 % en poids rapportés au dérivé de benzimidazole.
6. Procédé selon la revendication 5, caractérisé en ce que la matière de base est un hydroxyde ou un sel d'acide inorganique faible d'un métal choisi dans le groupe constitué par un métal alcalin, un métal alcalino-terreux et l'aluminium.
7. Procédé selon la revendication 5, caractérisé en ce que la matière de base est choisie dans le groupe constitué par un hydroxyde de magnésium d'alumine, un hydroxyde d'aluminium et un carbonate de magnésium.
8. Procédé selon la revendication 5, caractérisé en ce que la matière de base est un sel d'un acide organique avec un métal alcalin, un métal alcalino-terreux, l'aluminium et une amine.
9. Procédé selon la revendication 5, caractérisé en ce que la matière de base est choisie dans le groupe constitué par des amides, des acides amino basiques, des thiamines et des amines.
10. Procédé selon la revendication 5, caractérisé en ce que la matière de base est un sel d'acide gras supérieur d'un métal alcalin ou d'un métal alcalino-terreux.
11. Procédé selon l'une quelconque des revendications 5 à 10, caractérisé en ce que la matière de base est contenue dans une quantité non inférieure à 10 % en poids rapportés au dérivé de benzimidazole.
12. Procédé selon la revendication 11, caractérisé en ce que la matière de base est contenue dans une quantité de 10 à 200 % en poids rapportés au dérivé de benzimidazole.
13. Procédé selon l'une quelconque des revendications 5 à 12, caractérisé en ce que le dérivé de benzimidazole est sous la forme de particules ayant un diamètre moyen non supérieur à 10  $\mu$ m.